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PRIMARY CARCINOMA OF THE MALE URETHRA

HENRY A. R. KREUTZMANN, M.D.

AND

BEN COLLOFF, M.D.

SAN FRANCISCO

Since Hutchinson, in 1861, reported the first authentic case of primary carcinoma of the male urethra, no article on this subject has appeared in which the author personally reviewed all the preceding cases. In most instances the reports made by previous writers have been accepted without consulting the original sources. No doubt one of the reasons this has not been done is the fact that it is not always possible to obtain the original articles.

We have searched the entire literature and, except for a few papers, have been able to abstract the originals. As a result of our work, 32 additional cases have come to light which had not been mentioned in the literature since their publication. The total number of cases reported in the literature is 148 (see table).

LOCATION OF LESION

Carcinoma may occur in any of the anatomic divisions of the urethra. For clinical purposes we have listed the growths in two main groups, according to their location. In the first group are those occurring in the anterior, or penile, portion of the urethra, and in the second are those found in the bulbomembranous, or posterior, portion. Anatomically the bulbous portion is not a part of the posterior portion of the urethra, but it has been included because the symptoms and physical signs of tumors in this location are the same as those of growths occurring in the prostatic and membranous portions. In 65 patients the growth was in the anterior portion of the urethra; in 77 it was in the posterior portion. It is interesting to note that there is little difference in the incidence of carcinoma in the two portions of the urethra.

ETIOLOGIC FACTORS

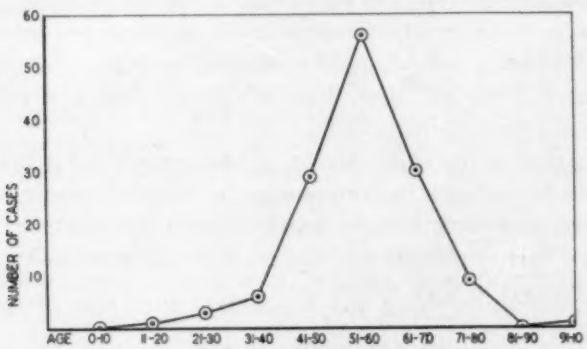
Urethral irritation evidently plays a part in the development of malignant tumor. The presence or absence of stricture was mentioned in 92

From the Department of Urology, the Mount Zion Hospital.

cases; in 76 per cent there was a positive history of this condition. In 7 the stricture was traumatic, and in 1 it was congenital. In Kretschmer's case the irritation was chemical, following the injection of Hartzell's solution [1] into the urethra. In 2 patients the growth was an adenocarcinoma, and the question arises whether one should consider such a tumor a true primary carcinoma of the urethra or analogous to the type of growth which develops originally in Cowper's gland and later involves the urethra.

AGE INCIDENCE

Carcinoma of the urethra may occur at any age, although the incidence (see chart) was highest in the fifth decade (56 patients). The youngest patient (Paton's) was 18 years old. Kroiss reported the case of the oldest patient, a man 91 years of age.



Age incidence of carcinoma of the male urethra.

PATHOLOGIC PICTURE

In many cases no pathologic report of the growth was made. The following list is a summary of the tumors which were examined, showing the types and incidence of each:

Squamous cell carcinoma or Epithelioma	101 cases
Papillary carcinoma	6 cases
Transitional cell carcinoma	3 cases
Adenocarcinoma	2 cases
Mucoid gland carcinoma	2 cases
Columnar cell carcinoma	1 case
Endothelioma	1 case

1. Hartzell's solution is made up as follows: iodine crystals, 50 grains (3.2 Gm.); zinc iodide, 15 grains (0.96 Gm.); potassium iodide, 15 grains (0.96 Gm.); water, ½ ounce (15 cc.), and glycerin, ½ ounce (15 cc.).

Watson, Lewis and Selvaggi reported cases in which the growth was limited to the prostatic portion of the urethra. Watson described the tumor in his case as an "irregular, lumpy growth arising from the floor and lateral walls of the urethra with excessive bleeding."

In most cases carcinoma of the posterior portion of the urethra presents itself as an abscess about the size of a walnut in the perineal region, elongated in the anteroposterior diameter. It is located in the median raphe, about 2 cm. posterior to the penoscrotal angle. This abscess, which appears as a small tumor-like mass, is tender and red. It discharges thick purulent material through a pinpoint opening. The abscess may heal completely for a time after treatment. It may recur, or it may never heal and may present infiltrated, indurated edges, with a few drops of urine appearing because of the fistulous connection.

The description of Bobbio's case is typical of the sequence of pathologic changes which occur when the posterior portion of the urethra is involved. At the first operation, incision of a perineal abscess was performed; healing was poor, with periurethral infiltration. A second operation was performed, with excision of the abscess together with the infiltrated periurethral tissue. Healing took place for a few weeks, after which the patient was readmitted to the hospital with a perineal fistula. After closure of the fistula the tumor reappeared. It was described as hard and painful. It was the size of an orange, with a shiny, dark bluish adherent skin. Where the skin was missing there were red cyanotic vegetations; in some places these were the size of peas. There were numerous small openings representing fistulous tracts. Incision of this mass revealed a cauliflower-like growth made up of large vegetations with a crater-like ulceration in the center. The skin at the periphery of the growth was cyanotic and at several points was stretched to the point of breaking. On section of the urethra there was observed infiltration into the corpora cavernosa, with complete ulceration of the bulbous portion of the urethra, so that it could not be distinguished from the surrounding neoplastic tissue.

In the anterior portion of the urethra one finds a nodule on the ventral surface of the penis, with or without one or more fistulous tracts. If the growth is at the fossa navicularis there may be an ulceration of the glans with a small pinpoint opening of the urinary meatus.

METASTASIS

Metastasis may occur via either the blood or the lymph channels. In the majority of the cases reported there was no mention of changes in the superficial inguinal glands. It is impossible, therefore, to summarize the incidence of involvement of these glands.

The drainage of the greater portion of the penile part of the urethra is to the deep subinguinal glands; that from the bulbomembranous portion, to the external iliac and hypogastric glands and from there to the

common iliac nodes. In some cases in which the inguinal glands were reported to be enlarged, later pathologic examination showed no malignant tissue but merely chronic adenitis. The size of the inguinal glands, therefore, is not a criterion of the pathologic process. The only metastasis in our second case was found in the lung. Metastasis to the scrotum or its contents is rare. We have been able to find only 1 case in which this occurred, that of Geissler, in which the epididymis was involved.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The possibility of carcinoma of the urethra should be considered in the case of a man over 40 who with no previous history of stricture has the symptoms characteristic of this condition. Progressive difficulty of urination is an outstanding symptom. Hematuria occurs infrequently—as a rule, only after instrumentation.

With carcinoma of the posterior portion of the urethra there is usually some progressive urinary difficulty, such as burning, frequent voiding or diminution in the size of the stream. Associated with these symptoms there may appear a soft, fluctuant periurethral mass. Incision of this mass gives only temporary relief. Healing does not take place; subsequent induration of the edges of the wound develops, and sloughing with suppuration occurs. Failure of any periurethral abscess to heal promptly should make one suspect malignant change.

In the anterior portion of the urethra the symptoms are the same. The fact that the patient himself feels a small mass in the penile segment of the urethra and consults a physician early is one of the reasons that the incidence of cures is largest when this is the region involved. If the growth involves the fossa navicularis, an ulcer, with or without a urinary fistula, may exist.

The final diagnosis must depend on urethroscopic examination. Polypoid tissue should be removed for biopsy. One must differentiate this condition from traumatic rupture of the urethra and also from simple stricture. A complete history together with a thorough urethroscopic and physical examination will rule out these conditions.

TREATMENT

Anterior Portion of the Urethra.—In 65 of the 148 cases studied the carcinoma occurred in the anterior portion of the urethra. Various methods of treatment were used, such as (1) partial or complete amputation of the penis, (2) total or partial emasculation, (3) roentgen treatment of the inguinal glands, (4) application of radium to the growth, (5) resection of the urethra and the growth, (6) external urethrotomy and (7) inguinal adenectomy in conjunction with one of the aforementioned forms of treatment.

Amputation of the penis, either complete or partial, was the treatment most often used. It was performed on 35 patients, resulting in 30 recoveries and only 5 deaths. Radium or roentgen therapy without surgical intervention was used for 3 patients, 2 of whom were cured.

When the growth is limited to the distal anterior portion of the urethra, that is, to the part in the region of the glans penis, partial amputation can be safely employed. If, however, the malignant process is in the shaft of the penis, near the bulb, and particularly if the corpora cavernosa are involved, it is best to perform radical amputation.

Emasculation is a needless operation and should never be done, as the testicles are not invaded metastatically. Infiltration of the scrotum with urine, due to rupture of the urethra, has been reported. This may have led some surgeons to perform total emasculation.

It is surprising to note that of the 65 patients in whom the anterior portion of the urethra was involved 35, or 54 per cent, recovered; 19, or 29 per cent, died, and in 11 cases, or 17 per cent, there was no mention of the end result.

Posterior Portion of the Urethra.—Seventy-seven patients had carcinoma of the posterior portion of the urethra; the growth was found most often in the bulbous or the membranous part but occasionally in the prostatic part. A study of the case histories showed many varied forms of treatment. Some, no doubt, were merely palliative, as the disease was too far advanced to permit constructive surgical intervention.

The different forms of treatment described are (1) suprapubic cystostomy, (2) internal urethrotomy, external urethrotomy or both, (3) incision and drainage of the perineum, (4) resection of the urethra and the growth, (5) fulguration and application of radium, (6) excision of the inguinal or of the deep femoral glands, (7) total emasculation, (8) passage of sounds and (9) use of an indwelling catheter.

In this series of 77 patients only 10, or 13 per cent, recovered, while 58, or 75 per cent, died. In 9 cases, or 12 per cent, there was no mention of the end result.

The operation which gave the greatest number of cures was resection of the urethra, including the growth. This was performed in 6 of the 10 cases. In 2 of the 6 the inguinal glands also were removed, in a third the penis was amputated and in a fourth radium was applied postoperatively.

In contrast to the gratifying end results obtained in the treatment of growths involving the anterior portion of the urethra, carcinoma of the posterior portion presents a gloomy picture. This is no doubt due to the fact that there are no characteristic symptoms of this disease. The patients are treated for stricture and its complications, such as rupture of the urethra, periurethral abscess or urinary fistula. By the time the true condition is recognized the growth has become inoperable.

Summary of One Hundred and Forty-Eight Cases of Carcinoma of the Male Urethra

Author	Age of Patient, Years	Complaints	Gonorrhea	Stricture	Location of Lesion	Treatment	Type of Growth	End Result
Hutchinson	22	Swelling and induration of penis; urinary fistula	NM	No	AU	Amputation of penis	Epithelial carcinoma	Cure
Billroth	50	Difficulty of urination; urinary retention	NM	NM	AU	None	No microscopic study	Death
Thiersch	60	Swelling in perineum; difficulty on urination; incontinence; multiple fistulas in right buttock	NM	Yes	MU	External urethrotomy	Epithelial carcinoma	Death
Mears	40	NM	NM	NM	AU	Tumor removed from meatus	Squamous cell carcinoma	NM
Schustler	72	Fever; difficulty of urination; swelling of penis and scrotum	NM	No	BU	External urethrotomy	Squamous cell carcinoma	Death
Poncet	56	Difficulty of urination; multiple fistulas	Yes	Yes	BU	Refused treatment	.....	NM
Grünfeld	50	Hematuria; difficulty of urination; urinary retention	NM	NM	BU	Passage of sounds; urethroscopy	NM	Death in 3 months (further treatment refused)
Guyon and Guiard	52	Difficulty of urination	Yes	Yes	BM	Internal urethrotomy; external urethrotomy	Squamous cell carcinoma	Death
Guyon and Guiard	60	Difficulty of urination; multiple perineal fistulas	Yes	Yes	MU	External urethrotomy	Carcinoma	Death
Trzebicky	68	Perineal abscess; scrotal fistula; swollen penis	No	Yes (traumatic)	BMU	Amputation of penis	Epithelial carcinoma	Death
Paul	54	Abscess of scrotum and perineum	NM	Yes	BMU	Drainage of abscess; division of stricture	Epithelioma	Cure in 2 months
Albert	55	Infiltration of perineum; perineal fistulas	NM	Yes	BU	Excision of tumor; resection of urethra	Carcinoma	Death
Poncet	60	Infiltration of urine; perineal abscess	Yes	Yes	BMU	Wide incisions	Carcinoma	Death
Griffith	70	Difficult and painful urination	No	No	BU and AU	External urethrotomy	Squamous cell carcinoma	Death
Witzenhausen	48	Difficulty of urination; perineal fistulas	No	Yes (traumatic in AU)	MU	External urethrotomy	Carcinoma	Death
Witzenhausen	55	Inguinal, perineal and scrotal fistulas	Yes	Yes	BMU	External urethrotomy	Epithelioma	Death
Beck	62	Difficulty of urination; swelling in perineum	Yes	Yes	BU	External urethrotomy	Squamous cell carcinoma	Discharge in 3 months; inguinal glands enlarging
Durante	56	Bloody discharge from urethra	NM	NM	AU	NM	Epithelioma	Death
Oberländer	72	Swelling in bulbous region	Yes	Yes	BU	Excision of urethra to external sphincter (inguinal glands also removed)	Squamous cell carcinoma	Cure
Albarran	43	Fistulas at base of penis	No	No	AU	Excision of penis, scrotum, testicles and inguinal glands	Squamous cell carcinoma	Death
Symonds	48	Hematuria; dysuria; frequency; tumor above pubes	NM	NM	Entire urethra, including bladder	Perineal cystostomy	Epithelioma	Death
Lowenthal	48	Perineal fistulas; difficulty of	No	Yes		None		

Symonds	48	Hematuria; dysuria; frequency; tumor above pubes	NM	NM	Entire urethra, including bladder	Perineal cystostomy	Epithelioma	Death
Lowenthal	48	Perineal fistulas; difficulty of urination	No	Yes (traumatic)	AU	None	Carcinoma	Death
Lowenthal	68	Swelling of perineum and scrotum, with fistulas; difficulty of urination	NM	NM	BU	Amputation of penis	Carcinoma	Death
Fuller	..	Retention of urine; urinary fistula	NM	NM	AU	NM	Cancer	Death
Cabot	"Elderly"	Painful swelling in perineum; perineal fistulas	Yes	NM	BU	Incision and exploration of perineal abscess	Cancer	Death
Buday	67	Difficulty in urination; fistulas in penile urethra	No	No	AU	Amputation of two thirds of penis	Cystopapillary cancer	NM
Chevereau	62	Dysuria; urinary fistula; tumefaction at base of scrotum	Yes	Yes	MU	Total emasculation	Epithelioma	Cure
Bazy and Carey	62	Tumefaction and fistula; difficulty and pain on urination	Yes	NM	Pars cavernosa, AU	Total emasculation	Epithelioma	.....
Wassermann	49	Perineal abscess; cystitis	Yes	Yes	MU	Internal urethrotomy	Squamous cell carcinoma	Death
Wassermann	67	Urinary infiltration of scrotum and penis	Yes	Yes	MU	Internal urethrotomy	Epithelioma	Death
Wassermann	53	Urinary infiltration	Yes	Yes	BU	Incision and dilation; resection	Epithelioma	Death
Wassermann	66	Difficulty of urination; perineal infiltration	NM	Yes	BMU	Incision	Epithelioma	Death
Hottinger	55	Dysuria; urethral discharge	NM	NM	AU	Amputation of penis	Squamous cell carcinoma	Cure
Hottinger	58	Urethral discharge; difficulty of urination; urinary fistula	NM	NM	AU	Amputation of penis	NM	Death
Van Hook	53	Bleeding from meatus; swelling and abscess posterior to glans penis	No	NM	AU	Amputation of penis; removal of inguinal glands	Carcinoma	.....
Bosse	25	Difficulty of urination	Yes	Yes	PU	External urethrotomy	Epithelioma	Death
Binaud and Chavannaz	54	Difficulty of urination; urinary retention; urinary extravasation through perineum	Yes	Yes	AU	Cystostomy; external urethrostomy	Epithelial carcinoma	Death
Scott	54	Difficulty of urination; dribbling; pain in penis	No	Yes	AU	Amputation of two thirds of penis; removal of inguinal glands	Carcinoma	Cure
Montgomery	54	Difficulty of urination; swelling in perineum; enlarging and ulcerating inguinal glands	No	NM	BU	Perineal incision	Squamous cell carcinoma	Death
Gayet	76	Bloody urethral discharge	Yes	Yes	AU	Perineal urethrotomy	Carcinoma with an unquestionable mucoid type of epithelium	Death
Soubeyran	64	Swelling of penis; difficulty of urination; hematuria	NM	?	AU	Amputation of penis	Epithelioma	Cure
Morestin	33	Lesion at meatus; dysuria	NM	NM	AU	None	Carcinoma (clinically)	NM

In this table the following abbreviations are used: BU, bulbous portion of urethra; MU, membranous portion of urethra; AU, anterior portion of urethra; PU, posterior portion of urethra; BMU, bulbomembranous portion of urethra, and NM, no mention.

Summary of One Hundred and Forty-Eight Cases of Carcinoma of the Male Urethra—Continued

Author	Age of Patient, Years	Complaints	Gonorrhea	Stricture	Location of Lesion	Treatment	Type of Growth	End Result
Morestin	47	Ulceration at meatus; dysuria; painful erections	NM	NM	AU	Amputation of half of penis	Epithelioma	Cure
Lipman-Wulf	50	Dysuria; difficulty of micturition; perineal swelling	NM	Yes (traumatic)	PU	Incision and drainage of perineum; removal of tissue	Epithelioma cell carcinoma	Death
Bobbio	53	Acute retention; perineal swelling; fistula	Yes	Yes	BU	Excision of fistula and granulation tissue	Epithelioma cell carcinoma	Death
Lavenant	48	Perineal swelling, with fistula	Yes	Yes	BMU	Incision and drainage	Epithelioma cell carcinoma	Death
Burkhardt	59	Difficulty of urination	Yes	Yes	15 cm. from meatus	NM	Carcinoma (flat cellular)	Death
Burkhardt	54	Difficulty of urination	Yes	Yes	12 cm. from meatus	NM	Carcinoma	NM
Hall	49	Perineal abscesses and fistulas	NM	NM	BU	Incision of abscess; excision of growth	Squamous cell carcinoma	Death
Wood	48	Chronic retention; swelling in the perineum	NM	No	BU	Incision of abscess	Squamous cell carcinoma	NM
Montgomery (personal communication to Hall)	53	NM	NM	NM	AU	Amputation of penis	Squamous cell carcinoma	Cure
Lecene	48	Dysuria; circular ulceration at surface of meatus; infiltration of glans penis	NM	NM	AU	1903, removal of ulcer and roentgen treatment; 1905, amputation of penis	Epithelioma	Cure
Shattock	54	Hematuria; dysuria; narrowing of urethra	No	NM	NM	Amputation of anterior portion of penis	Squamous cell carcinoma	NM
Platt	59	Difficulty of urination; urinary fistula near meatus	NM	Yes (traumatic)	AU	Amputation of penis	Epithelioma	Cure
Rupke	46	Chills and fever; perineal swelling; fistulas	No	NM	BU	External urethrotomy	Squamous cell carcinoma	Death
Rupke	38	Dysuria; hematuria; weak urinary stream	No	Yes (congenital)	BMU	External urethrotomy	Squamous cell carcinoma	Death
Preiswerk	83	Difficulty of urination; induration in perineum	Yes	Yes	BMU	Excision of growth; external urethrotomy; amputation of penis	Squamous cell carcinoma	Death
Preiswerk	61	Chills and fever; dysuria; weak stream; pain at base of penis	Yes	Yes	MU	Perineal incision and drainage	Carcinoma	Death
Alsberg-Delbanco	49	No urinary symptoms	?	NM	AU	Amputation of penis	Squamous cell carcinoma	Cure
Barney	62	Acute retention	No	Multiple	BU	Perineal section	Epithelioma	Death
Barney	58	Abscess in perineum	Yes	Yes	BMU	Indwelling catheter	Epithelioma	NM
Tizon	57	Difficulty of urination; infected ulceration near meatus	Yes	Yes	AU	Amputation of penis; excision of inguinal glands	Epithelioma	Cure
Olivier and Clunet	52	Difficulty of urination; closure of meatus; urinary fistula near glans	NM	NM	AU	Extirpation of involved portion of urethra	Epithelioma	Cure

Olivier and Clunet	52	Difficulty of urination; closure of meatus; urinary fistula near glans	NM	NM	AU	Extirpation of involved portion of urethra	Epithelioma	Cure
Englisch	57	Weak stream; perineal fistula following external urethrotomy	Yes	Yes	MU	Incision and drainage of perineal fistulas	Carcinoma	Death
Englisch	40	Chills and fever; multiple anterior urethral abscesses; enlarged inguinal glands	Yes	?	AU	NM	Squamous cell carcinoma (autopsy)	Death
Englisch	..	History of case lost	....	....	BMU	.....	Epithelial carcinoma	Death
Conporti	60	Pain and difficulty of urination; urinary fistula	Yes	NM	AU	Total emasculation	Squamous cell carcinoma	Cure
Mark	24	NM; diagnosis made by urethroscopy	NM	NM	AU	NM	NM	NM
Bonzani	63	Difficulty of urination; urinary retention; extravasation of urine	NM	NM	AU	Amputation of penis	Squamous cell carcinoma	Cure
Peacock	74	Difficult and painful urination; slight balanitis	NM	NM	AU	Amputation of half of penis	Epithelioma	Cure
Menard	57	Difficult and painful urination; hard infiltration of meatus	Yes	Yes	AU	Amputation of penis; excision of inguinal glands	Pavement cell epithelioma	NM
Ottow	69	Induration of urethra, near frenum; urethral discharge; difficult micturition	Yes	No	AU	Amputation of penis	Squamous cell carcinoma	Cure
Allenbach	51	Priapism	No	No	Entire U. mm. involved	Suprapubic cystostomy; incision into corpora cavernosa	Columnar cell carcinoma	Death
Kroiss	91	None given	NM	NM	AU	None	Squamous cell carcinoma	Death
Thaler	NM	Difficulty of urination; swelling of glans; purulent discharge	No	NM	AU	Amputation of penis	NM	Cure
Jaeger	NM	Indurated mass of 2 years' duration; urinary fistula; bleeding from meatus	NM	NM	AU	Amputation of penis	Carcinoma	Cure
Leipziger	53	Weakness of urinary stream; chills and fever; hematuria	No	NM	MU	Resection of urethra	Squamous cell carcinoma	Death, 3 weeks later of alcoholic delirium
Bierbaum	53	Chills and fever; weak stream; swelling in perineum	No	No	BMU	Suprapubic cystostomy; ext. urethrotomy; later, excision of BU and MU	Squamous cell carcinoma	Death
Menocal	70	Difficulty of urination; urethral fistulas; pain and induration of inguinal glands	No	NM	AU	Complete emasculation; excision of inguinal glands	Epithelioma	Cure
Albrecht	49	Swelling to right of bulbous urethra	NM	No	BU	Amputation of penis; excision of inguinal glands	Carcinoma	Death
Michon	NM	Painful and difficult urination; edema of scrotum; tumefaction in perineum	Yes	Yes	BMU	External urethrotomy; total emasculation	NM	Death
Amadeo	53	Difficulty in urination; swelling and fistulas in perineum	Yes	Yes	BMU	Internal urethrotomy incision of perineum	Epithelioma	Death

Summary of One Hundred and Forty-Eight Cases of Carcinoma of the Male Urethra—Continued

Author	Age of Patient, Years	Complaints	Gonorrhea	Stricture	Location of Lesion	Treatment	Type of Growth	End Result
Müller	58	Nodules along penile urethra	Yes	Yes	AU	Internal urethrotomy; resection of 4 cm. of urethra	Carcinoma	Death
Rizzi	49	Growth extending from meatus	Yes	Yes	AU (spread to bulbous urethra)	Removal of penis and portion of mem. urethra	Squamous cell carcinoma	NM
Oniel	64	Difficult and painful urination; perineal mass; acute retention	Yes	Yes	BU	Suprapubic cystotomy; perineal incision	Epidermoid carcinoma	Death
Oniel	51	Pain in penis on pressure; difficulty in starting stream; pain and fistula in perineum	Yes	Yes	AU (from bladder to scrotum)	Incision and curettage of abscess walls	Epithelioma	Death
Imbert	NM	Difficulty of urination; perineal infiltration	NM	NM	NM	Passage of sounds	NM	NM
Scholl and Braasch	48	Swelling of perineum; symptoms of stricture	Yes	Yes	BMU	Excision of growth; reconstruction of urethra; radium therapy	Squamous cell carcinoma	Cure
Culver and Forster	71	Difficult urination; swelling of penis	NM	NM	AU	Amputation of penis	Papillary carcinoma	Cure
Kretschmer	58	Swelling, induration and tenderness of shaft of penis, with fistula formation	NM	NM	AU	Amputation of penis, excision of inguinal glands	Papillary carcinoma	Cure
Uchida	56	Difficult urination; swelling of scrotum; swelling of penis; anuria	Yes	Yes	BU	Total emasculation	Carcinoma	Death
Laurie	52	Urethral discharge with blood; dysuria	No	NM	BU	External urethrotomy; incision of perineal abscess	Squamous cell carcinoma	Death
Paine	55	Difficult and painful urination; acute retention	Yes	Yes	AU	Incision of penoscrotal abscess; amputation of penis	Papillary carcinoma	Death
Paton	18	Swelling in perineum	No	No	BU	None	Carcinoma	Death
Diehl	50	Difficulty of urination; swelling in perineum	NM	NM	BMU	None	Epithelial cell carcinoma	Death
Diehl	57	Dysuria; swelling in perineum; swelling of right testicle	Yes	Yes	BMU	Incision and drainage; roentgen therapy	Epithelial carcinoma	Death
Christen	56	Multiple abscesses and fistulas of perineum and scrotum	Yes	Yes	AU	External urethrotomy; roentgen therapy	Squamous cell carcinoma	NM
Joly	60	Incontinence (late); acute retention; periurethral abscess	NM	Yes	BU	Internal urethrotomy; suprapubic cystotomy; amputation of penis and scrotum	Squamous cell carcinoma	Cure
Young and Davis	58	Acute retention; perineal and scrotal tumefaction; perineal fistula	NM	Yes, traumatic	MU	Incision of abscesses; perineal urethrotomy	Squamous cell carcinoma	Death
Young and Davis	46	Chills and fever; perineal	NM	NM	MU	Incision of abscesses	Squamous cell carci-	Death

Young and Davis.....	58	Acute retention; perineal and scrotal tumefaction; perineal fistula	NM	Yes, traumatic	MU	Incision of abscesses; perineal urethrotomy	Squamous cell carcinoma	Death
Young and Davis.....	46	Chills and fever; perineal abscesses and fistulas	NM	NM	MU	Incision of abscesses	Squamous cell carcinoma	Death
McCune.....	47	Difficulty of urination; acute retention	Yes	Yes	BU	Urethral dilatation; roentgen therapy; suprapubic cystostomy	Epidermoid carcinoma	NM
Fukai-Yoshida.....	56	Dysuria; weak stream	No	No	AU	Amputation of penis	Carcinoma	Cure
Wurmser.....	37	Perineal swelling; later, abscess and fistula formation	Yes	NM	BMU	Excision of perineal fistula; incision of abscess	Epithelioma	Death
Marion.....	42	Urinary abscess and fistula	NM	NM	BMU	Opening of abscess; radium therapy	Epithelioma	Death
Marion.....	46	Pain in bulbous region	NM	NM	BU	Cystostomy; resection by circular urethrorrhaphy	Epithelioma	Death
Desnos.....	NM	NM	NM	NM	NM	Internal urethrotomy; perineal incision	Epithelioma	Death
Robb.....	69	Acute retention; indurated mass in perineum; enlargement of both testes	No	NM	BU	Amputation of penis; splitting of scrotum	Transitional cell carcinoma	Death
Robb.....	59	Small hard nodule at penoscrotal junction; palpable mass in bulbous urethra	Yes	Yes (instrumented 477 times)	BMU	Complete emasculation	Transitional cell epithelioma	Death
Bieberbach and Peters...	42	Difficulty of urination; acute retention	NM	Yes (traumatic)	BMU	Perineal incision and drainage	Epidermoid carcinoma	Death
Bieberbach and Peters...	62	Pus and blood in urine; urinary fistula	Yes	Yes	MPU	Incision and drainage; of perineum; application of radium	Epidermoid carcinoma	Death
Agrifoglio.....	52	Difficulty of urination; swelling of perineum	Yes	No	BMU	Radium; suprapubic cystostomy	Squamous cell carcinoma	Death
Watson.....	36	Hematuria; difficulty in starting stream	Yes	NM	PU (prostatic)	Suprapubic cystotomy; diathermy; implantation of radium	.....	.....
Watson.....	73	Sensation of obstruction near meatus	Yes	Yes	AU (fossa navicularis)	Radium; roentgen therapy	Mucous membrane epithelioma	Cure
Lagleyze.....	42	Periurethral abscess near glans penis; urethral induration to penoscrotal junction	?	?	AU	Amputation of penis; excision of inguinal glands	Squamous cell carcinoma	Cure
Flamm.....	50	Hemorrhage from meatus; growth protruding from meatus	Yes	No	AU	Amputation of penis after radium application	Squamous cell epithelioma	Cure
Huggins and Curtis.....	59	Mass in perineum	Yes	Yes	AU	Amputation of penis	Squamous cell carcinoma	Cure
Bedrna.....	57	Dysuria	No	No	AU	Extirpation of urethra; roentgen rays to inguinal glands and perineum	Adenocarcinoma	Cure

Summary of One Hundred and Forty-Eight Cases of Carcinoma of the Male Urethra—Continued

Author	Age of Patient, Years	Complaints	Gonorrhea	Stricture	Location of Lesion	Treatment	Type of Growth	End Result
Geissler	64	Perineal fistula	NM	NM	MU, PU	External urethrotomy	Epithelial carcinoma	Death
Lower	58	Acute retention; chills and fever; perineal fistula	No	Yes	MU	Suprapubic cystotomy; resection of urethra	Squamous cell carcinoma	Cure
Lower	42	Acute retention	Yes	Yes	Indurated area in perineum ? BMU	Suprapubic puncture; resection of urethra; roentgen therapy	Papillary carcinoma	Cure
Lower	61	Difficulty of urination; induration in perineum	Yes	Yes	AU	Total emasculation; inguinal glands removed	Adenocarcinoma	Cure
Beck	64	Weakness of urinary stream for two years	Yes	No	AU	Suprapubic cystostomy; resection of portion of penis involved	Squamous cell carcinoma	Death 1 year later
Sokolov	59	Difficulty of urination; acute retention	NM	NM	AU	Resection of urethra; removal of inguinal glands	Mucoid glandular carcinoma	Cure
Kirwin	62	Acute retention; enlarged inguinal glands, preventing stooping	Yes	No	AU	Growth removed by cautery; inguinal masses dissected; radon seeds	Epithelioma	No metastasis; recurrence 4 months later
Potel and Houplin	64	Ulcer at meatus	NM	NM	AU	Partial amputation of penis	Squamous cell carcinoma	NM
Boggon	60	Bloody discharge from meatus	Yes	NM	AU	Amputation of penis	Squamous cell carcinoma	.....
Lazarus	53	Indurated area in penis; lymphedema of skin and scrotum	Yes	NM	MU	Amputation of penis; inguinal and deep glands excised	Squamous cell carcinoma	Cure
McNally	62	Frequency of urination; painful swelling of perineum	Yes	Yes	BMU	Incision and drainage of perineum; external urethotomy; suprapubic cystostomy	Squamous cell carcinoma	Death
Astraldi	74	Painful and difficult urination; enlargement of scrotal raphe	NM	NM	AU	Suprapubic cystostomy; amputation of penis	Squamous cell carcinoma	Cure
Goldstein and Abeshouse	66	Pain on urination; discharge of pus and blood; tissue protruding from meatus; enlargement of glans and corpora cavernosa	No	Yes	AU	Incision and drainage of abscess in cavernosa; suprapubic cystotomy; radical resection, including lymphatics	Transitional cell carcinoma	Death
Chute	69	Unpleasant sensation at head of penis; incontinence; difficulty of urination	No	No	AU	Complete emasculation	Squamous cell carcinoma	Cure
Chute	70	Swelling and induration of perineum, perineal fistula	NM	Yes	BMU	Inoperable	No sections made	Death
Larsen	48	Difficulty of urination; mass in perineum	NM	Yes (traumatic)	PMU	Inoperable	Carcinoma	Death
König	49	Difficulty of urination; chills and fever; urinary infiltration, with fistula	Yes	Yes	MU	Excision of mass; amputation of penis	Epithelioma	Death
Selvaggi	52	Urinary retention; tumefaction to perineal urethra; acute pains to perineum; ulceration and	Yes	Yes	MU	Urethral catheter (in dwelling); later, total emasculation	Epithelioma	NM

König	49	Difficulty of urination; chills and fever; urinary infiltration, with fistula	Yes	Yes	MU	Excision of mass; amputation of penis	Epithelioma	Death
Selvaggi	52	Urinary retention; tumefaction to perineal urethra; acute pains to perineum; ulceration and fistula; fetid purulent discharge	Yes	Yes	MU	Urethral catheter (indwelling); later, total emasculation	Epithelioma	NM
Deveze	50	Urinary retention; swelling and urinary infiltration of perineum	Yes	Yes	BU	External urethrotomy; removal of growth; amputation of penis one month later	Epithelioma	Cure
Mercier	59	Painful urination; perineal tumefaction	Yes	Yes	BU	Internal urethrotomy; incision of perineum; radium	Epithelioma	NM
Dobrzaniecki	59	Difficulty of urination; painful urination	No	No	AU	Amputation of one third of penis; inguinal glands removed	Endothelioma originating from blood vessels	Cure
Mortenson	64	Acute retention; difficulty in starting stream; dribbing; periurethral abscess	NM	Yes	AU	Incision of abscess; suprapubic cystostomy	Squamous cell carcinoma	Death
Meland	55	Incontinence; bloody, purulent discharge; dysuria	No	No	BU	Amputation of penis plus suprapubic cystotomy; inguinal adenectomy later; roentgen therapy	Squamous cell carcinoma	Cure
Miller	78	Narrowing stream; dysuria; tumor in penis	No	No	AU	Palliative	Carcinoma of urethra	Death
Foulds	68	Soreness of penis; moderate enlargement of distal third; papillary growth on separating edges of urethra	NM	NM	AU	Biopsy; total amputation of penis; excision of inguinal and femoral nodes; transplant of urethra to perineum	Epithelioma	Cure
Foulds	64	Painful swelling of perineum; chills and fever	NM	Yes	BU	Incision of abscess; suprapubic cystotomy; palliative therapy	Squamous cell carcinoma	Death
Lewis	77	Swelling on ventral surface of penis; urinary fistula; hematuria and dysuria	NM	Yes	AU	Meatotomy and sounds; biopsy; radical amputation of penis with urethral transplant	Squamous cell carcinoma	Cure
Lewis	53	Painful urination; difficult dilatation of strictured area; loss of weight	Yes	Yes	PU	Cystotomy; radium	Papillary carcinoma	NM
Fernandez	60	Phlyctenule near meatus; enlarging posteriorly; (improved under antisyphilitic therapy); purulent secretion	Yes	NM	AU	Partial amputation of penis	Flat cell carcinoma	NM
Harbach	47	Swelling of penis; hematuria; pyuria; periurethral abscess; urinary fistula	Yes	NM	AU	Incision and drainage; partial amputation of penis; inguinal adenectomy	Squamous cell carcinoma	Cure
Townsend and Mulcahy	56	Swelling of perineum; terminal hematuria; difficult dilatation of urethra	Yes	Yes	BU	Roentgen therapy	Epidermoid carcinoma	Death
Kreutzmann and Colloff	52	Weak stream; frequent dilations; periurethral abscess following biopsy	Yes	Yes	AU	Cystostomy; incision, abscess; ureteral transplant (2 stage)	Epidermoid carcinoma	Died
Kreutzmann and Colloff	44	Weakness of urinary stream; pain and swelling at base of penis; later, perineal fistulas	Yes	Yes	PU	External urethrotomy; suprapubic cystostomy; incision, inguinal abscess; biopsy, urethral growth	Squamous cell carcinoma	Died

In reviewing the entire series of 148 cases, we were interested to note that inguinal glands had been removed in only 20 cases, 16 of anterior and 4 of posterior urethral involvement. Of the 45 patients in the entire series who recovered, inguinal adenectomy had been performed on only 13. In several patients the glands were seen on clinical examination to be enlarged. Sections after removal showed inflammatory changes but no metastasis.

Despite the fact that inguinal adenectomy was performed on only approximately 4 per cent of the patients who recovered, surgical intervention should include removal of the inguinal glands in order to obviate the possibility of metastasis by way of the lymphatics. Huggins and Curtis described the surgical procedure in detail, and repetition at this time is needless.

SUMMARY AND CONCLUSIONS

Primary carcinoma of the male urethra is a rare disease, only 148 cases having been previously reported. Of the total number of growths, 65 originated in the anterior and 77 in the posterior portion of the urethra. In 6 cases the location with reference to the site of origin of the growth was not mentioned. Two new cases bring the total to 150.

A thorough search of the literature revealed many cases which have not been mentioned since their original publication.

The greatest incidence of carcinoma of the male urethra is in the fifth decade.

In 88 per cent of the cases in which a pathologic report was made the tumor was a squamous cell carcinoma.

The inguinal glands are rarely involved, and in many cases enlargement is due to infection rather than to metastasis.

The treatment of carcinoma involving the anterior portion of the urethra which has given the greatest number of cures is partial or complete amputation of the penis.

The best results when the malignant process involved the posterior portion. were obtained by resection of the urethra with the included growth.

Inguinal adenectomy is advisable in all cases.

Sufficient data have not been obtained up to the present time to enable one to evaluate roentgen and radium treatment without previous surgical intervention.

2000 Van Ness Avenue.

490 Post Street.

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PANCREATICOGASTROSTOMY

EXPERIMENTAL TRANSPLANTATION OF THE PANCREAS INTO THE STOMACH

E. COOPER PERSON JR., M.D.
AND
FRANK GLENN, M.D.
NEW YORK

HISTORICAL CONSIDERATIONS

The early work of Brunner [1] in 1682, as reported by Ceccherelli, demonstrated that partial extirpation of the pancreas did not impair the health and digestion of the experimental animal. This salient observation has led to the development of surgical procedures which have been successful as long as the main pancreatic and biliary ducts have been left intact. However, investigations concerning the feasibility of attacking the head of the pancreas and thereby excluding the external pancreatic secretion from the intestinal tract have led to conflicting results.

A historical survey of these related experimental problems shows that the conflicts date from early time.

The first experimental approach to this subject was carried out by Bernard.[2] He occluded the pancreatic ducts by injecting them with paraffin and observed a marked disturbance in the absorption of fat from the intestinal tract, with early death of the animal. From this observation he concluded that pancreatic juice is highly essential for digestion. This conclusion was refuted by a number of investigators, namely, Schiff,[3] Cohnheim [4] and Martinotti,[5] who excluded the pancreatic enzymes from the intestinal tract in various ways and found that digestive functions continued in a satisfactory manner.

From the Department of Surgery of the New York Hospital and the Cornell University Medical College.

1. Brunner, C. L., cited by Ceccherelli, A.: La chirurgica du pancreas, Comptes rendus de la Congrès internationale de mèdicin, Paris, 1900, p. 159.

2. Bernard, C.: Mémoire sur le pancréas et sur le rôle du suc pancréatique dans les phénomènes digestifs, particulièrement dans la digestion des matères grasses neutres, Paris, J. B. Baillière, 1856.

3. Schiff, 1862, cited by Oser, in Nothnagel, H.: Encyclopedia of Practical Medicine, translated by A. Stengel, Philadelphia, W. B. Saunders Company, 1903.

4. Cohnheim, J., 1882, cited by Senn.[6]

5. Martinotti, G.: Sulla extirpazione del pancreas, Gior. d. r. Accad. di med. di Torino **36**:348, 1888.

The extensive and enlightening studies of Senn [6] demonstrated that the pancreas could be subjected to direct surgical procedures. He concluded, however, that complete resection of the head of the pancreas with the common duct is not justifiable and that procedures on this portion of the gland should be limited to partial excision with preservation of the common duct; he further accentuated his opinion by stating that if disease develops in this region it "precludes the propriety of operation." However, Nemier [7] presented a review of clinical surgical treatment of the pancreas and concluded that radical intervention for malignant lesions of this organ is surgically feasible. He referred to the need of establishing a communication between the pancreas and the intestine and cited Codivilla's case in which this procedure was carried out successfully.

Nemier's review and the further observation that pancreatectomy is followed by enormous loss of fat and nitrogen in the stools (Abelmann [8]; de Dominicis [9]; Sandmeyer [10]) probably led Biondi [11] to perform an experimental investigation with the purpose of establishing a new exit for the external secretion of the pancreas. Biondi implanted the transected portion of the pancreas and duct of Wirsung into the duodenum, but was unsuccessful. The 6 dogs which he subjected to this procedure died of peritonitis and gangrene of the small intestine. Similar results were obtained by Ceccherelli, who used 2 dogs. Both experimentalists concluded that the theory of pancreatic transplant is tenable but the procedure technically not feasible.

In an attempt to clarify the diverse conclusions reached regarding the effects of excluding the pancreatic enzymes, Lombroso [12] in 1908 repeated his work of 1894 (in Minkowski's clinic). He demonstrated that with the external secretions of the pancreas completely excluded the absorption of food is adequate and compatible with life. In con-

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7. Nemier, H.: Chirurgie de pancréas, Rev. de chir. **13**:618, 757 and 1007, 1893.

8. Abelmann, M.: Ueber die Ausnutzung der Nahrungsstoffe nach Pankreasextirpation mit besonderer Berücksichtigung der Lehre von der Fettresorption, Inaug. Dissert., Dorpat, C. Mattiesen, 1890.

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11. Biondi, D.: Contributo clinico e sperimentale alla chirurgia del pancreas, Clin. chir. **4**:131, 1896.

12. Lombroso, U.: Kann das nicht in den Darm sezernierende Pankreas auf die Nährstoffresorption einwirken? Arch. f. exper. Path. u. Pharmakol. **60**:99, 1908.

tradiction to this, Pratt, Lamson and Marks [13] proved that animals show a markedly diminished absorption of fat and nitrogen, as evidenced by large residues demonstrated in the stools by careful chemical analysis.

The excellent article by Desjardins [14] on pancreatectomy reintroduced the feasibility of radical operative intervention for carcinoma of the head of the pancreas. For the first time the surgical procedure was designed in accord with the complex physiologic and anatomic character of the gland and with full recognition of the tremendous difficulties encountered in such an approach. Desjardins claimed that the key to radical operations on the pancreas is duodenal resection and restoration of the communication between the pancreas and intestine. He found it essential to restore the continuity of the pancreatic flow in order to avoid the danger of intra-abdominal leakage from the pancreatic stump or the formation of a pancreatic retention cyst. As a result of his thorough investigation, Desjardins offered a two stage procedure for radical removal of a malignant lesion of the head of the pancreas. The two stages consisted in (*a*) reestablishment of the continuity of the intestinal and biliary tracts and (*b*) resection of the duodenum and the head of the pancreas and restoration of the flow of pancreatic secretions by pancreaticojejunostomy.

A few months after Desjardins' publication, Sauvé [15] presented an article approving the logic of a pancreaticoduodenostomy as a necessary step in radical procedures involving the head of the pancreas. However, he claimed that to reestablish the communication between the pancreas and intestine was ideal but not surgically practical at the time. He provided instead an extra-abdominal outlet for the retained pancreatic secretions by attaching the pancreatic stump to the anterior abdominal wall, thus creating a pancreatic fistula.

In 1909, Coffey [16] reported the first successful experimental transplantation of the pancreas into the jejunum and described the difficult and intricate technic by which it was accomplished. This procedure, which he called "pancreaticoenterostomy," consisted of uniting a loop of jejunum in the form of a U after the manner of a Finney pyloroplasty and implanting the stump of the pancreas into this loop. His technic was complicated and difficult because he assumed that in order to prevent leakage it was necessary to bring the transplanted pancreas into contact with a considerable area of serosal surface. Coffey concluded that pan-

13. Pratt, J. H.; Lamson, P. D., and Marks, H. K.: The Effect of Excluding Pancreatic Juice from the Intestine, Tr. A. Am. Physicians **24**:266, 1909.

14. Desjardins, A.: Technique de la pancréatectomie, Rev. de chir. **1**:945, 1907.

15. Sauvé, L.: Des pancréatectomies et spécialement de la pancréatectomie céphalique, Rev. de chir. **37**:113, 1908.

16. Coffey, R. C.: Pancreato-Enterostomy and Pancreatectomy: A Preliminary Report, Ann. Surg. **50**:1238, 1909.

creaticoenterostomy is feasible surgically and that the implanted pancreas in animals showed no pathologic changes up to the time the animals were killed (thirty days). These observations were verified by Sweet and Simons [17] and by Patrie, Pyle and Vale,[18] who used a less complicated technic.

Concurrently with these surgical efforts, further problems associated with the exclusion of the external secretion of the pancreas from the intestinal tract were being studied. Fisher [19] and also Allen, Bowie, McLeod and Robinson [20] demonstrated the presence of fatty infiltration and degenerative changes of the liver in pancreatectomized animals at death. Hershey and Soskin [21] (1932) confirmed this work and found that death of the animal could be prevented if the diet included phospholipids, such as lecithin and choline, or raw pancreas. Berg and Zucker [22] deprived the dogs of pancreatic enzymes by means of a modified Elman-McCaughon pancreatic fistula and consistently found marked hepatic changes. The authors concluded that the underlying common factor was exclusion of the external secretion from the intestine.

Contradicting results were obtained by Van Prohaska, Dragstedt and Harms [23] on the basis of their experiments which showed that the external secretion of the pancreas played no role in preventing fatty infiltration and degeneration of the liver. They observed that changes in the liver did not occur in dogs provided with total pancreatic fistulas or in dogs with ligated pancreatic ducts and degeneration of the pancreatic parenchyma. They proposed the existence of a new hormone concerned in some manner with the normal transport and utilization of fat.[24] On the other hand, Ralli, Rubin and Present [25] were unable to

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17. Sweet, J. E., and Simons, I. H.: Some Experiments on the Surgery of the Pancreas, Ann. Surg. **61**:308, 1915.

18. Patrie, H. H.; Pyle, L. A., and Vale, C. F.: Recent Experimental Studies on the Pancreas, Surg., Gynec. & Obst. **24**:479, 1917.

19. Fisher, N. F.: Attempts to Maintain the Life of Totally Pancreatectomized Dogs Indefinitely by Insulin, Am. J. Physiol. **67**:634, 1924.

20. Allen, F. N.; Bowie, J. J.; McLeod, J. J. R., and Robinson, W. L.: Behavior of Depancreatized Dogs Kept Alive with Insulin, Brit. J. Exper. Path. **5**:75, 1924.

21. Hershey, J. M., and Soskin, S.: Substitution of "Lecithin" for Raw Pancreas in the Diet of the Depancreatized Dog, Am. J. Physiol. **98**:74, 1931.

22. Berg, B. N., and Zucker, I. F.: Liver Changes After Deprivation of External Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **29**:68, 1931.

23. Van Prohaska, J.; Dragstedt, L., and Harms, H. P.: The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatized Dog, Am. J. Physiol. **117**:166, 1936.

24. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in the Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**: 175, 1936.

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support the contention of Dragstedt and his associates concerning a fat-metabolizing hormone produced by the pancreas. They concluded the findings of Dragstedt and his co-workers may have been due to the short period the animals were under observation (four to twelve weeks). Here may be mentioned also the work of Best and Ridout [26] and that of MacKay and Barnes [27] on rats. These investigators observed that the pancreatic extract described by Dragstedt exercised such lipotropic effects as could be expected from its choline and protein content.

Chaikoff, Connor and Biskind [28] were able to keep dogs alive for five years after complete pancreatectomy by feeding a special diet supplemented by insulin. Their extended observations demonstrated a sequence of striking changes in the liver; namely, fatty infiltration, hyaline degeneration and atrophy of the hepatic cells at the periphery of the lobules and fibroblastic proliferation ending with the typical fibrotic lesion of cirrhosis. Boyce and McFetridge [29] made an experimental study of the operative procedures which involve exclusion of the pancreatic secretion from the intestinal tract, with special reference to the metabolism of the liver cell. They concluded that when partial pancreatectomy is a necessary part of the operation for malignant disease of the ampulla and periampullary regions, fatty metamorphosis of the liver will occur unless provisions are made to prevent it.

In summarizing this historical survey it may be stated:

1. In the surgical treatment of malignant lesions of the pancreas, loss of the pancreatic enzymes should be avoided if a practical means is available to reintroduce them into the intestinal tract.

2. Exclusion of pancreatic secretion from the intestinal tract does not appear seriously to interfere with normal digestion.

3. Marked changes in the liver, such as fatty infiltration and degeneration, occur when the intestinal tract is deprived of pancreatic secre-

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25. Ralli, E. P.; Rubin, S. H., and Present, C. H.: The Liver Lipids and Fecal Excretion of Fat and Nitrogen in Dogs with Ligated Pancreatic Ducts, Am. J. Physiol. **122**:43, 1938.

26. Best, C. H., and Ridout, S. H.: The Pancreas and the Deposition of Fat in the Liver, Am. J. Physiol. **122**:67, 1938.

27. MacKay, E. M., and Barnes, R. N.: Influence of a Pancreas Extract and Other Proteins on Liver Fat and Ketosis, Proc. Soc. Exper. Biol. & Med. **38**:410, 1938.

28. Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin, Am. J. Path. **14**:101, 1938.

29. Boyce, F. F., and McFetridge, E. M.: An Experimental Study of Operations Which Involve Exclusion of the Pancreatic Secretion from the Intestinal Tract, with Special Reference to the Possible Effects on Protein and Fat Digestion and on the Metabolism of the Liver Cell, Surgery **4**:51, 1938.

tion over a long period. A dietary safeguard may be found in such substances as lecithin, choline and raw pancreas (or alcoholic extracts of pancreas).

4. It is well to keep in mind Handelsman's [30] warning that great care must be given to a study of the literature before accepting or rejecting one observer's opinion concerning the external secretion of the pancreas and the effects of the absence of these enzymes from the intestinal tract.

Malignant lesions of the ampulla of Vater and of the head of the pancreas present a common therapeutic problem both from the anatomic and the physiologic standpoint. Radical operation for lesions affecting these structures seems justified, for without it a fatal outcome is inevitable and usually rapid. However, the effects of radical extirpation on the physiologic function of neighboring organs must be seriously considered. The most important of these adjacent structures are the pancreatic duct and the common duct. In a radical procedure these ducts must be sacrificed, with resulting exclusion of the enzymes of the pancreas and of the bile from the intestinal tract. The opinion that complete deprivation of pancreatic secretion is not detrimental remains open to controversy; therefore it seemed important to study the feasibility of reintroducing this secretion. Were it possible to devise a practical procedure to accomplish this, several purposes would be served:

1. If an outlet for the pancreatic secretion were provided, there is every reason to believe that the pancreas would retain its normal function.

2. It would prevent the fatty infiltration and degenerative changes in the liver which experimental observations lead one to expect after exclusion of the pancreatic secretion from the intestinal tract. These pathologic alterations of the liver interfere with its normal function and increase the danger of intercurrent systemic infection.

3. The external secretion from the pancreas amounts at least to 700 to 800 cc. daily. This secretion continues to amount to 200 to 300 cc. in spite of the parenchymatous atrophy and fibrosis of the gland associated with partial occlusion of the duct. Surgical attempts to curb this secretion merely by ligation of the duct without providing a suitable outlet are impractical and are likely to lead to pancreatic fistula, pancreatic abscess or hemorrhagic pancreatitis, all serious conditions in an already debilitated patient.

4. As a preliminary step to radical operation it would appear beneficial to reintroduce the pancreatic enzymes into the intestinal tract, since

30. Handelsman, M. B.: The Digestive and Absorptive Function of the External Secretion of the Pancreas, Ann. Int. Med. **11**:1479, 1938.

pancreatic insufficiency seems to be one of the most significant factors in the symptomatology and the rapid terminal course of malignant tumors of this region.

Fear of the well known complications acute pancreatitis and peritonitis following operations on the pancreas in man has given this organ the reputation of a surgical "noli me tangere." Judd and Hoerner [31] enumerated other factors which have retarded progress in surgical treatment of the pancreas, such as the generally poor condition of the patient, the insidious onset of the disease, the relative inaccessibility of the lesions, the intimate relation to major abdominal structures which cannot be sacrificed and the extreme technical difficulties of any surgical procedure in this region. Yet efforts to create a new outlet for the secretions of the pancreas have not been abandoned.

PURPOSE, METHOD AND RESULTS OF THE EXPERIMENTAL STUDY

The first successful transplant of the pancreas into the stomach was carried out by Tripodi and Sherwin [32] in 1934. Prior to that operation the small intestine usually had been selected as the site for the implant, but Tripodi and Sherwin chose the stomach because of its greater accessibility and size and in order to prevent obstruction of the lumen of the bowels and strangulation of the transplanted pancreas. In addition, the acid content of the stomach reduces but does not completely destroy the activity of the pancreatic enzymes, thus decreasing the potential danger of pancreatitis. These investigators gave a detailed account of the technic by which the pancreatic stump was transplanted into the posterior wall of the stomach through a triradiate incision with invaginated serosal surfaces.

Because this was a blind method of transplantation, experimental work was undertaken to find a means by which the operation could be accomplished under direct vision.

When the problem was approached in experimental animals, it was realized that there are minor but significant anatomic variations between the human and the canine pancreas.[33] The most important of these is the presence in the dog of a protective peritoneal covering over the organ, the absence of which in the human being subjects him to greater danger of spreading infection. To simulate as nearly as possible the condition found in man, this protective peritoneal covering can be stripped off the pancreas in dogs.

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31. Judd, E. S., and Hoerner, M. T.: Surgical Treatment of Carcinoma of the Head of the Pancreas and of the Ampulla of Vater, Arch. Surg. **31**:937 (Dec.) 1935.

32. Tripodi, A. M., and Sherwin, C. F.: Experimental Transplantation of the Pancreas into the Stomach, Arch. Surg. **28**:345 (Feb.) 1934.

33. Bradley, O. C.: Topographical Anatomy of the Dog, New York, The Macmillan Company, 1927.

Technic.—The peritoneal cavity was opened through an upper right rectus incision, and the first portion of the duodenum and the attached pancreas were delivered. The main and accessory ducts and their entrance into the duodenum were exposed by carefully freeing the duodenum from the adherent pancreatic tissue. The main pancreatic duct, which corresponds to the duct of Santorini in man, was doubly ligated and divided. Stay sutures of arterial silk were placed in the lateral walls of the remaining accessory duct (duct of Wirsung), and it was divided (fig. 1). These sutures afforded a means of traction, so that the organ could be manipulated without traumatizing the friable pancreatic tissue.

The pancreas was then transected just distal to the accessory duct. (This division must be carried out with care in order to identify the central duct and to control bleeding from the pancreaticoduodenal vessels which traverse the superior border of the gland.) The stump of the pancreas, consisting of the neck and

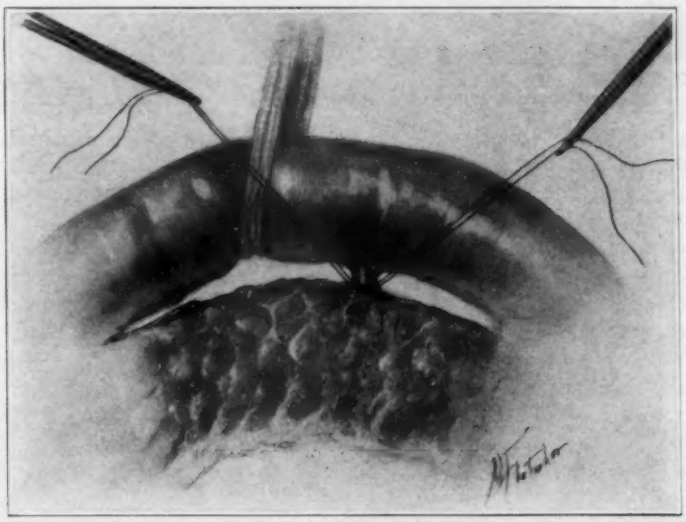

Fig. 1.—Exposure of the main and accessory ducts and their entrance into the duodenum. The ducts are exposed by carefully freeing the duodenum from the adherent pancreatic tissue. The dotted lines indicate transection of the pancreas.

body and the ducts, was implanted into the stomach under direct vision in this manner (fig. 2):

A longitudinal incision was made in the anterior wall of the stomach, midway between the greater and lesser curvatures and close to the pylorus (fig. 3). With a finger in this opening to direct further procedures, the stomach was rotated so that a transverse incision might be made in the posterior wall, opposite the first opening (fig. 3). This was approximately 2 cm. in length and lay near the pylorus.

Silk stay sutures were passed through each side of the stump of the pancreas at a point 1 cm. from the transected end, care being taken to avoid puncturing the pancreatic duct or vessel. These stay sutures were brought into the stomach through the posterior stoma, threaded into needles and returned to the outside by passing through the entire thickness of the gastric wall at a point 1 cm. from

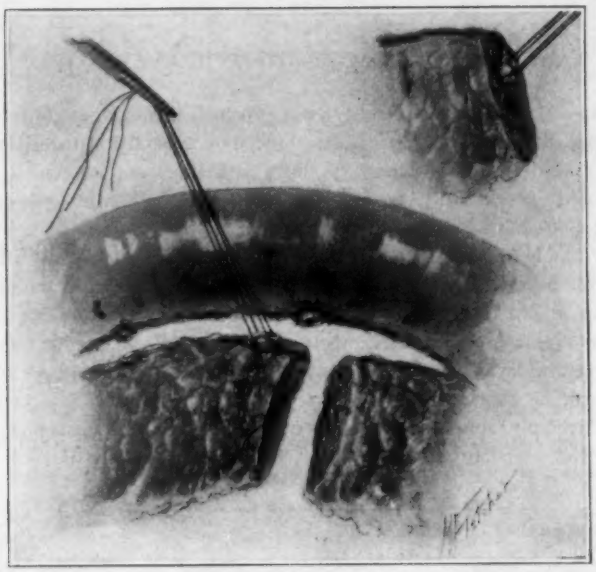

Fig. 2.—Pancreas transected. The main pancreatic duct is visualized.

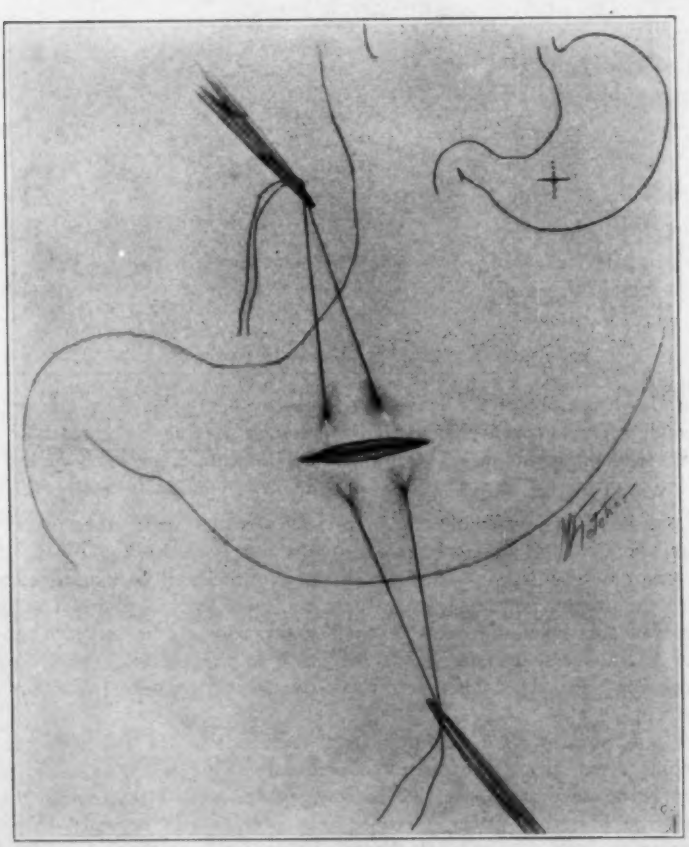

Fig. 3.—Longitudinal incision in the anterior wall of the stomach, midway between the greater and lesser curvature near the pylorus. The dotted line (insert) indicates the incision on the posterior gastric wall.

the opening (fig. 4). The stay sutures attached to the pancreatic duct were also brought through into the stomach and subjected to tension through the anterior incision in the gastric wall, thus drawing the stump well into the gastric lumen. With this traction maintained, the pancreas was anchored into position by tying the sutures which passed through the wall of the stomach (fig. 5). This resulted in an everted approximation of the gastric wall to the pancreatic parenchyma. Additional sutures were introduced at either end of the incision to fix it permanently in place. The abdomen was closed with silk without drainage.

Results and Comment.—In this series of experiments 32 dogs were used. The first 12 dogs were subjected only to pancreaticogastrostomy as described. The method proved to be entirely satisfactory and surgically feasible. For this reason it was instituted in the remaining dogs as a preliminary step in operations on the ampulla of Vater and the head of the pancreas. One dog died of acute hemorrhagic pancreatitis on the third day after the transplant, owing to a technical error. Six dogs were killed at appointed times to determine microscopically the condition of the pancreatic parenchyma and to confirm the chemical indications that the pancreatic duct remained patent. Proof of the patency of the duct was obtained by injecting fluid into the caudal end of the pancreatic duct and observing its free flow into the stomach.

Death subsequent to further surgical procedures occurred in 17 animals. The duration of life after operation varied from five to one hundred and seven days. Complete postmortem examinations were made routinely. In the majority of instances death was due to bronchopneumonia, perforation of a jejunal ulcer or intussusception. Eight dogs were still alive from forty-eight to one hundred and sixty-nine days after the two stage procedure.

Tables 1 and 2 present data on 6 dogs which survived and 6 which died. These animals were subjected to the following two stage procedures: first stage, pancreaticogastrostomy, cholecystogastrostomy and ligation of the common duct, and second stage, resection of the head of the pancreas and duodenum and gastroenterostomy.

The purpose of the first stage of the procedure was to create a new channel for bile and pancreatic secretions into the gastrointestinal tract. In performing the pancreaticogastrostomy, an exploratory incision in the anterior wall of the stomach constituted one step; this anterior aperture was used as a stoma for the cholecystogastrostomy. An interval of from ten to twenty-five days elapsed between the first and the second stage of the operation.

In every instance marked atrophy and fibrosis of the head of the pancreas were found at the second operation. This pathologic alteration was due to the inadequate blood supply to the remaining portion of the pancreas—the result of ligating the pancreaticoduodenal vessels during the transsection of the gland at the first operation. On the other hand, the flow of blood through the implanted portion of the pancreas was sufficient to permit the organ to function normally during the life of the animal. This was determined by chemical tests and confirmed by the absence of atrophy and fibrosis at postmortem examination.

All the dogs subjected to this experiment were placed on a standard diet [34] supplemented by vitamins B, C and D. They all remained active and well, and

34. This was a basal diet, given on the basis of 80 calories per dog per kilogram of body weight. The approximate ratio was 50 to 60 Gm. of carbohydrates, 20 to 25 Gm. of fat and 18 to 25 Gm. of protein. This was supplemented by vitamins in the form of yeast (brewers'), cod liver oil and tomato juice administered daily. Lecithin, choline and extracts of the pancreas were not given.

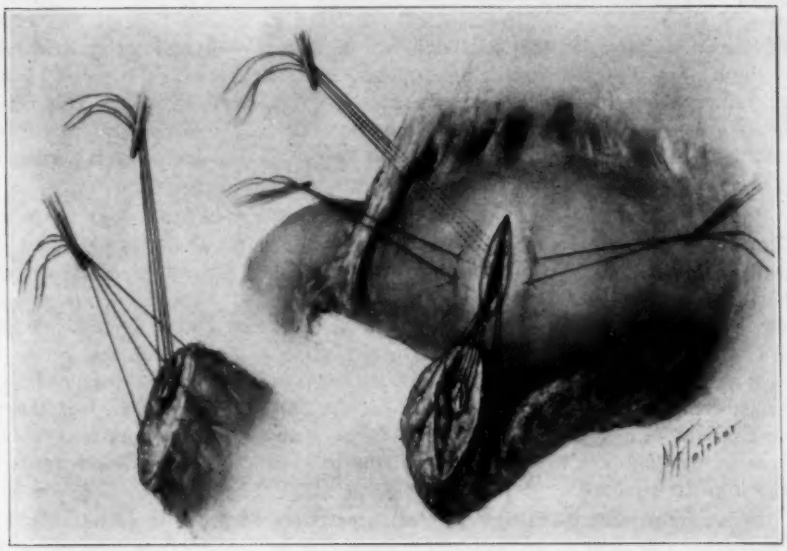

Fig. 4.—Rotation of the stomach and placing of an incision in the posterior gastric wall. The pancreas is delivered into the stomach by means of stay sutures.

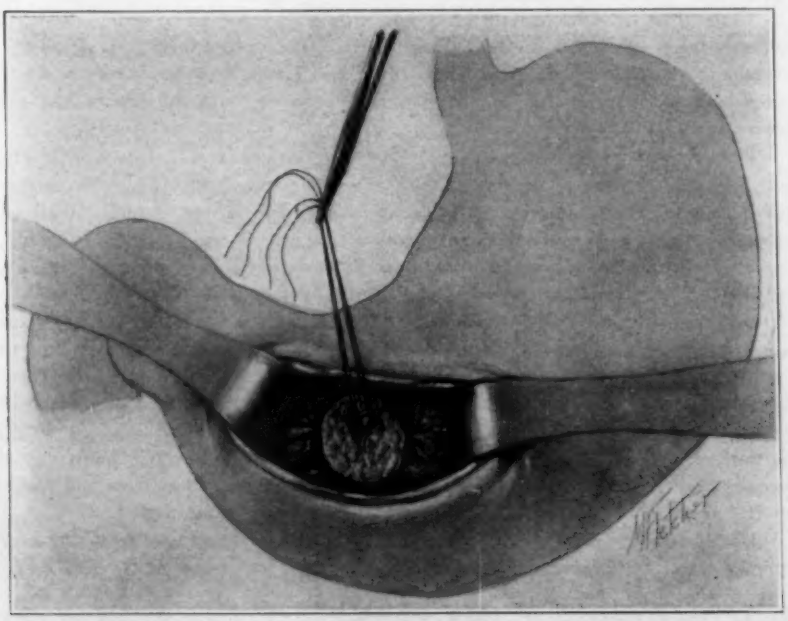

Fig. 5.—Transected end of the pancreas transplanted into the stomach through the posterior wall. The arterial silk sutures are on the transected pancreatic duct.

TABLE 1.—*Data on Six Dogs Which Survived*

	Hepatic Analysis			Pancreatic Examination	
	Chemical Analysis		Microscopic Examination		
	Lipid (Quantitative)				

TABLE 1.—*Data on Six Dogs Which Survived*

Dog No.	Initial Weight	Present Weight	Days Alive	General Health	Chemical Analysis			Hepatic Analysis				Pancreatic Examination at Reexploration (Gross)
					Gastric Lipase	Blood Sugar	Urinalysis	Lipid (Quantitative) Percentage	Lipid (Quantitative) Days After Operation	Microscopic Examination Hematoxylin and Eosin	Microscopic Examination Fatty Infiltration	
240	22 pounds (10 Kg.)	22 pounds (10 Kg.)	169	Good	Yes	Normal	No sugar	6.2	140	Normal	No	Normal
251	20 pounds (8.2 Kg.)	18 pounds (8.2 Kg.)	126	Good	Yes	Normal	No sugar	3.6	90	Normal	No	Normal
333	30 pounds (13.6 Kg.)	23 pounds (10.4 Kg.)	90	Poor (jejunal ulcer)	Yes	Normal	No sugar	5.4	57	Normal	No	Normal
327	27 pounds (11.3 Kg.)	25 pounds (11.3 Kg.)	88	Good	Yes	Normal	No sugar	4.8	40	Normal	No	Normal
330	28 pounds (12.7 Kg.)	23 pounds (10.4 Kg.)	82	Fair	Yes	Normal	No sugar	7.0	60	Normal	Slight	Slight atrophy with fibrosis
372	24 pounds (10.9 Kg.)	20 pounds (9.1 Kg.)	48	Good	Yes	Normal	No sugar	5.2	30	Normal	No	Normal

TABLE 2.—*Data on Six Dogs Which Died*

Dog No.	Initial Weight	Weight Before or After Death	Days Alive	Chemical Analysis			Hepatic Analysis			Postmortem Examination of Pancreas		Cause of Death
				Gastric Lipase	Blood Sugar	Urinalysis	Lipid (Quantitative) Percentage at Death	Microscopic Examination Hematoxylin and Eosin	Microscopic Examination Fatty Infiltration	Gross	Microscopic	
268	17 pounds (7.7 Kg.)	14 pounds (6.4 Kg.)	107	Yes	Normal	No sugar	4.4	Normal	No	Normal, pancreatic duct patent	Normal	Pneumonia
280	20 pounds (9.1 Kg.)	18 pounds (8.2 Kg.)	96	Yes	Normal	No sugar	4.2	Normal	No	Normal, pancreatic duct patent	Normal	Perforated jejunal ulcer
254	34 pounds (15.4 Kg.)	28 pounds (12.7 Kg.)	75	Yes	Normal	No sugar	6.2	Early degeneration	Slight	Slight atrophy, pancreatic duct patent	Increase connective tissue	Pneumonia
267	23 pounds (10.4 Kg.)	19 pounds (8.6 Kg.)	75	Yes	Normal	No sugar	5.2	Normal	No	Normal, pancreatic duct patent	Normal	Perforated jejunal ulcer
340	28 pounds (12.7 Kg.)	22 pounds (10 Kg.)	70	Yes	Normal	No sugar	5.0	Normal	No	Normal, pancreatic duct patent	Normal	Pneumonia
219	20 pounds (9.1 Kg.)	19 pounds (8.6 Kg.)	66	Yes	Normal	No sugar	5.5	Normal	No	Normal, pancreatic duct patent	Normal	Intussusception

Fig. 6.—Fixed specimen ninety-six days after pancreaticogastrostomy. Note the normal appearance of the transplanted pancreas with the orifice of the duct cannulized. (The intragastric portion of the pancreas was digested in twenty to twenty-five days.)

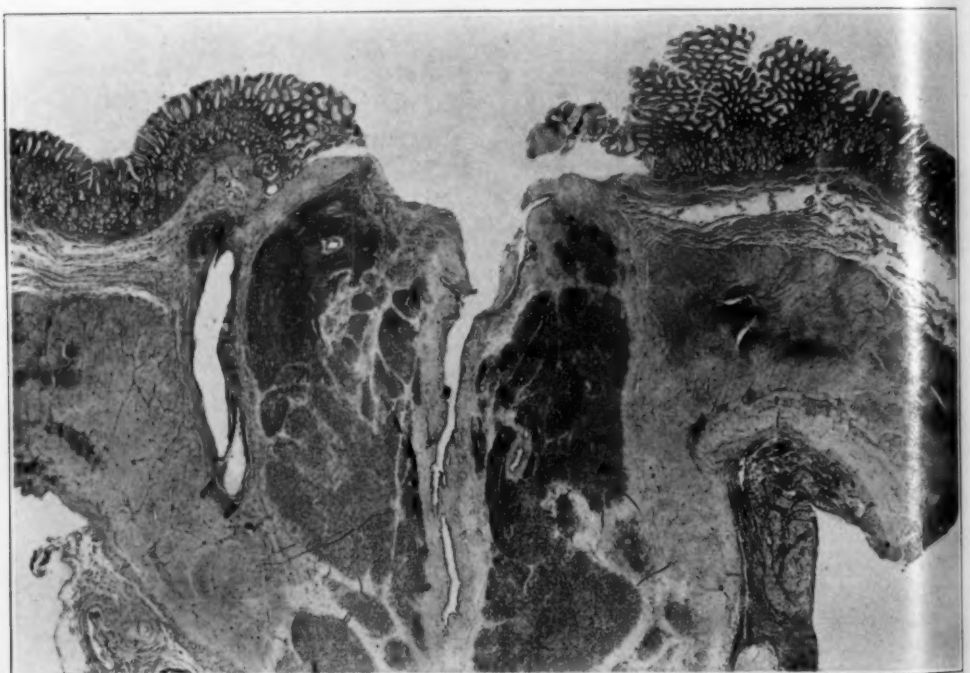

Fig. 7.—Photomicrograph of a section through the site of the pancreatic implant. Note that the pancreatic implant is firmly united to the muscularis of the gastric wall. The patent pancreatic duct entering the lumen of the stomach is easily demonstrable. The mucosa surrounding the orifice of the duct appears normal.

they remained within 5 pounds (2.3 Kg.) of their initial weight except the animals in which a jejunal ulcer developed after the two stage procedure.[35]

After the pancreaticogastrostomy, at intervals of ten to one hundred and forty days, analyses of the gastric contents and of the urine were made, and the value for blood sugar was determined. Since the gastric contents invariably revealed

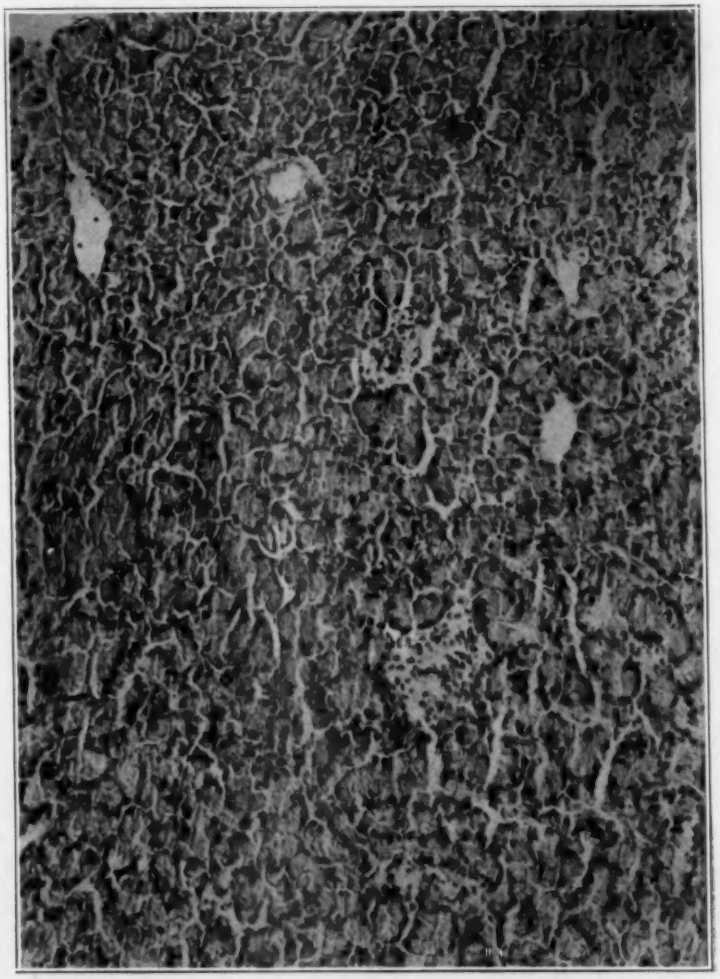

Fig. 8.—Photomicrograph of the pancreas seventy-five days after pancreaticogastrostomy. The pancreas retains its normal architecture. There is no evidence of atrophy or increase in connective tissue.

the presence of active pancreatic lipase, it must be concluded that the pancreatic secretion reached the stomach. At no time were there more than negligible changes

35. Eiselberg (cited by Markowitz, J.: Textbook of Experimental Surgery, New York, William Wood & Company, 1937) found that jejunal ulcers developed in over 25 per cent of animals subjected to pyloric exclusion and gastroenterostomy.

in the value for blood sugar, and repeated analyses of the urine failed to reveal the presence of sugar.

When the abdomen was opened after the first operation or at a specific date to obtain biopsy tissue from the liver, inspection of the site of transplantation revealed a normal-appearing pancreas without perceptible atrophy, firmly united

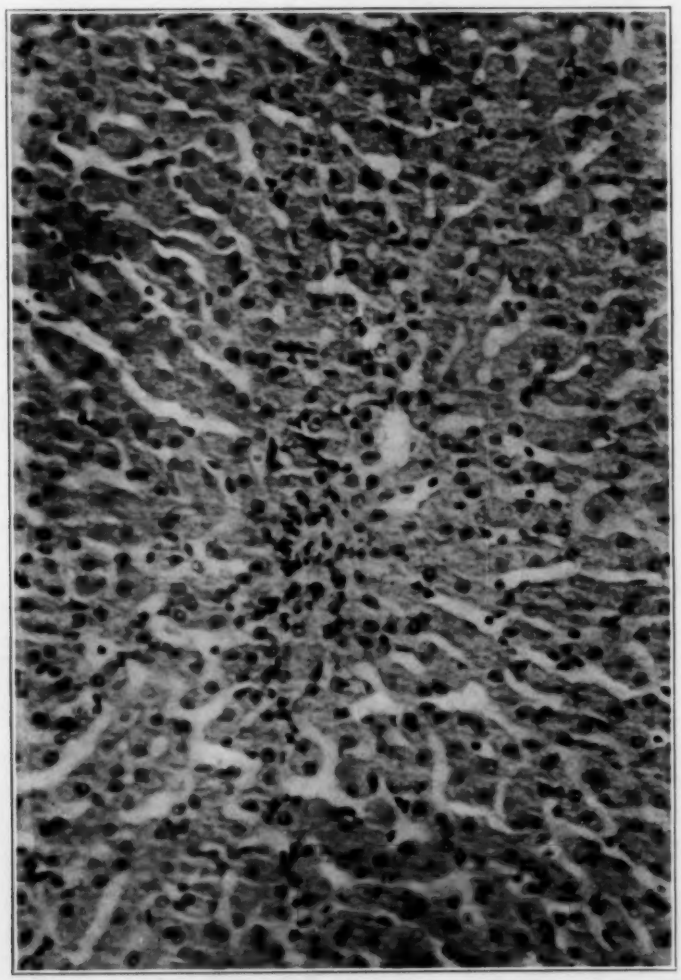

Fig. 9.—Photomicrograph from a section of the liver one hundred and forty days after pancreaticogastrostomy. The liver retains its normal topography. There is no evidence of fatty infiltration or degeneration.

to the stomach. It was found that the excess intragastric pancreatic tissue projecting into the stomach after implant was digested in twenty to twenty-five days, but the orifice of the duct remained patent (fig. 6).

On microscopic examination serial sections through the site of the pancreatic implant revealed connective tissue union between the pancreas and the musculature

of the gastric wall. The pancreatic acini appeared orderly and without evidence of cellular dissociation or inflammatory cell infiltration. The islets of Langerhans appeared normal. The mucosa around the patent orifice of the pancreatic duct was not ulcerated and appeared normal (figs. 7 and 8). It is known that the liver assimilates fat if the intestinal tract is deprived of the external secretion

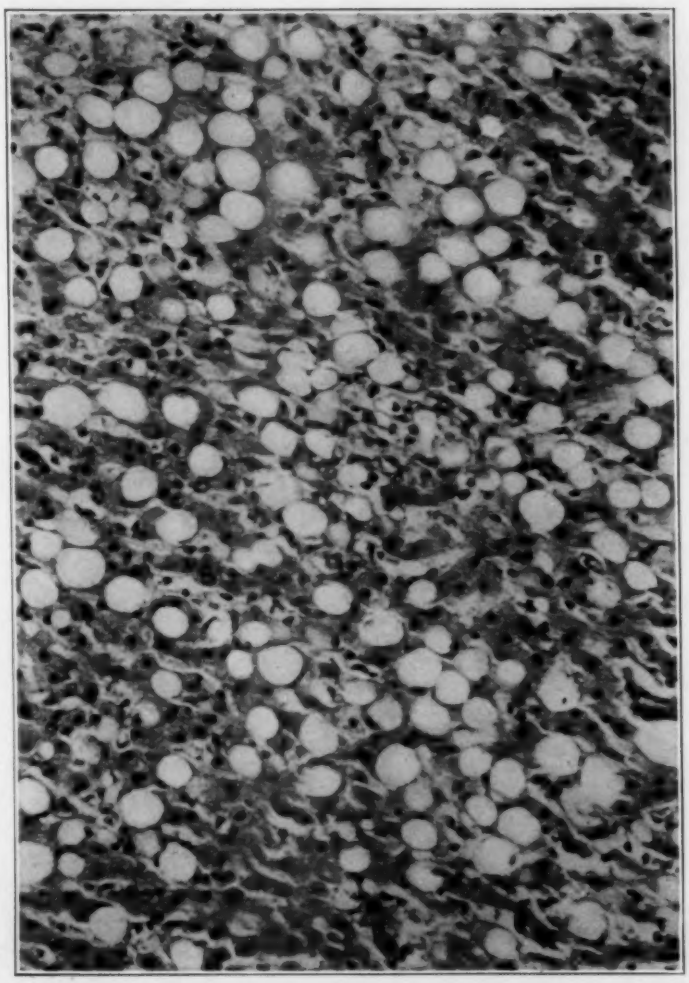

Fig. 10.—Photomicrograph from a section of the liver sixty days after ligation, division of the pancreatic ducts and partial pancreatectomy. The normal hepatic architecture is hardly discernible, owing to fatty acid infiltration and degenerative changes in the hepatic cell.

of the pancreas. Therefore, 3 to 10 grains (0.19 to 0.65 Gm.) of tissue for biopsy was taken from the liver at intervals of ten to one hundred and forty days after the first stage procedure and subjected to chemical and microscopic examination

for lipid deposition to determine whether the implanted pancreatic gland continued to function. With the Bloor [36] method and a simplified method introduced by Kaplan and Chaikoff [37] the fatty acid content of the liver was found to vary from 3.6 to 6.7 per cent in the "transplant" animals, as compared with the normal value of 3 to 5 per cent.

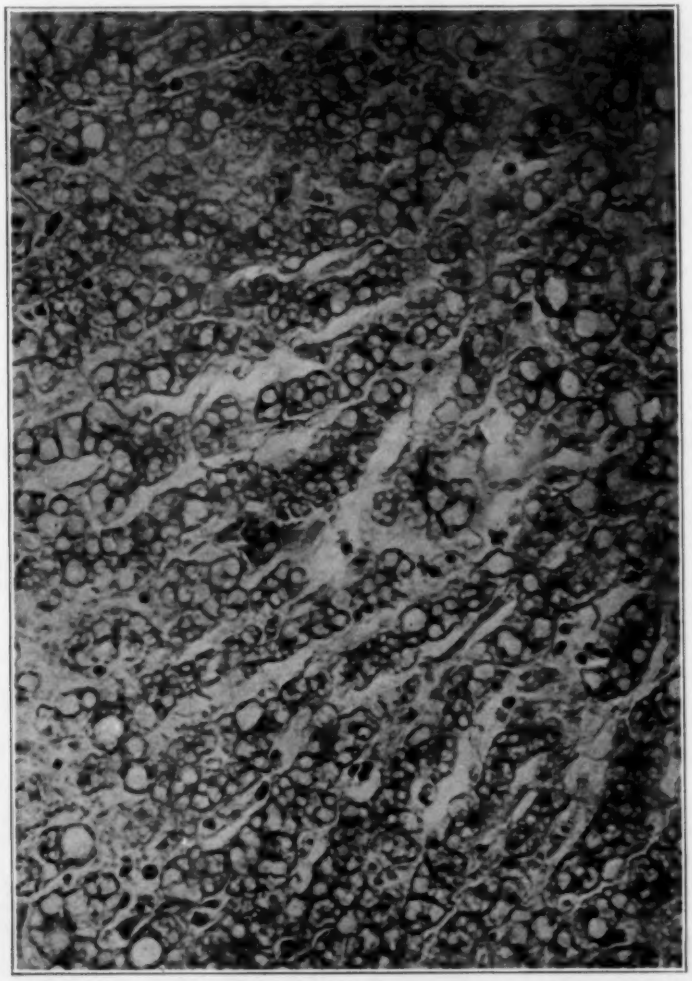

Fig. 11.—Photomicrograph from a section of the liver ninety days after ligation, division of the pancreatic ducts and pancreatectomy. Note the advanced vacuolation and the degenerative changes in the hepatic cell.

Microscopic section of the liver treated with special stains (nile blue sulfate and sudan III) confirmed these quantitative results, since there was no infiltration of the liver cells with fat. Examination with routine stains (hematoxylin and

36. Bloor, W. R.: Oxidative Determination of Phospholipid (Lecithin and Cephalin) in Blood and Tissues, J. Biol. Chem. **82**:273, 1929.

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eosin) showed that the cords and cells of the liver had retained their normal orderly arrangement. There was little cellular infiltration and no evidence of cellular degeneration (fig. 9).

In order to study the effects of complete exclusion of the external secretion of the pancreas from the intestinal tract, animals were subjected to ligation and

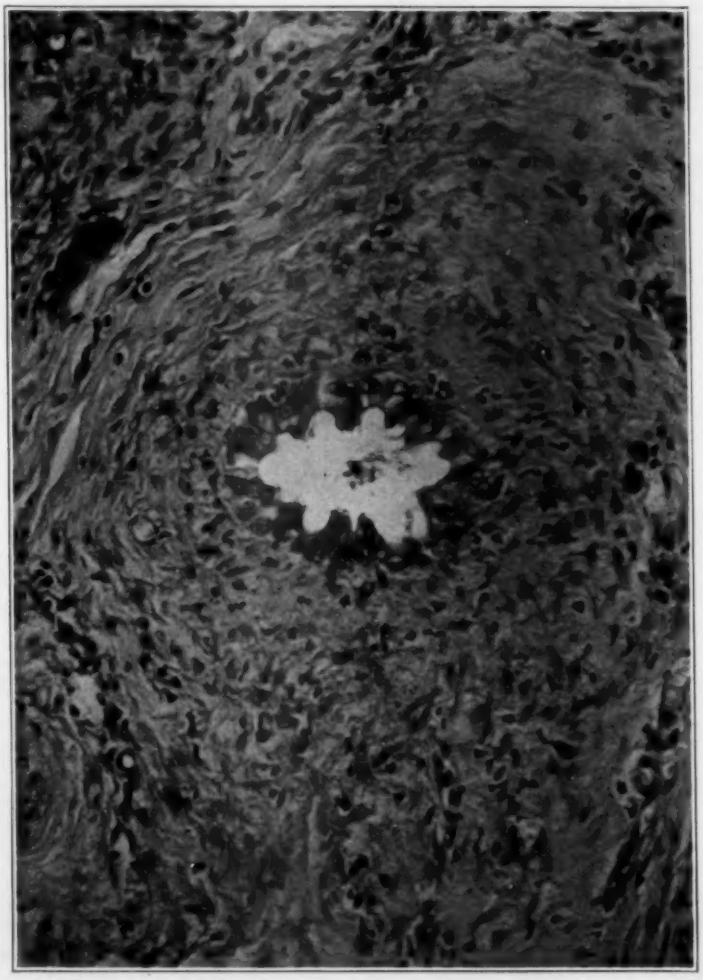

Fig. 12.—Photomicrograph of the pancreas sixty days after ligation, division of the pancreatic ducts and partial pancreatectomy. There are marked dilatation of the pancreatic ducts and destruction of acini by invading connective tissue.

division of the pancreatic ducts and partial pancreatectomy. The amount of gland resected corresponded as closely as possible to that removed in the "transplant"

37. Kaplan, A., and Chaikoff, J. K.: Liver Lipids in Completely Depancreatized Dogs Maintained with Insulin, J. Biol. Chem. **108**:201, 1935.

animals, but the stump was reenforced with omentum and left in situ instead of being transplanted into the stomach. The various secondary procedures which formed a part of the completed operation in the first series of animals were carried out on these 6 dogs also. The animals were subjected to cholecystogastrostomies, duodenal resections and gastroenterostomies in either two or three stages, but they showed less tolerance for these interventions than did the "transplant" animals. Although their diet was the same, these dogs lost weight and exhibited a syndrome consisting of anorexia, exhaustion, intermittent vomiting and foamy stools. Pancreatic lipase was not present in the gastric contents; the values for blood sugar

Fig. 13.—Fixed specimen one hundred and seven days after the completed two stage procedure. The photograph shows the site of the pancreatic implant and the stomas of cholecystogastrostomy and gastroenterostomy.

remained within normal limits in spite of the marked pancreatic atrophy; quantitative determinations of the lipid content of the liver showed an increase in fatty acid as high as 8 to 18.4 per cent. Microscopic studies of the livers of these dogs revealed diffuse fatty infiltration of the hepatic cells, and routine stains demonstrated extensive cellular dissociation. The normal hepatic architecture was hardly discernible. The liver cells were transformed into large vacuoles with small, peripherally placed nuclei. The degenerative changes were diffuse but seemed to be more marked in the periphery of the lobule (figs. 10 and 11).

TABLE 3.—*Data on Six Dogs Subjected to Ligation and Division of the Pancreatic Ducts and Partial Pancreatectomy Without Transplantation of the Pancreatic Stump into the Stomach*

Dog No.	Initial Weight	Weight Before or After Death	Days Alive	Post-operative Course	Chemical Analysis			Hepatic Analysis			Postmortem Examination of Pancreas		Cause of Death
					Gastric Lipase	Blood Sugar	Urinalysis	Lipid, Percentage at Death	Microscopic Examination: Hematoxylin and Eosin	Microscopic Examination: Fatty Infiltration	Gross	Microscopic	
260	33 pounds (15 Kg.)	23 pounds (10.4 Kg.)	93	Poor	No	Normal	No sugar	8	Slight atrophy with degeneration	++	Pancreatic cyst with atrophy	Chronic pancreatitis with cyst	Pneumonia
299	38 pounds (17.2 Kg.)	27 pounds (12.2 Kg.)	60	Poor	No	Normal	No sugar	12	Atrophy with with cellular dissociation	+++	Atrophy	Chronic pancreatitis with atrophy and fibrosis	Cachexia
307	22 pounds (10 Kg.)	16 pounds (7.3 Kg.)	41	Fair	No	Normal	No sugar	9.6	Moderate degeneration	++	Atrophy with pancreatic cyst	Chronic pancreatitis	Perforated jejunal ulcer
288	28 pounds (12.7 Kg.)	20 pounds (9.1 Kg.)	36	Poor	No	Normal	No sugar	11.2	Degeneration and atrophy	++	Atrophy	Chronic pancreatitis	Pneumonia
111	18 pounds (8 2 Kg.)	16 pounds (7.3 Kg.)	33	Poor	No	Normal	No sugar	11.2	Slight degeneration	+++	Atrophy	Chronic pancreatitis	
295	39 pounds (17.7 Kg.)	36 pounds (16.3 Kg.)	10	Poor	No	Normal	No sugar	18.4	Degeneration and atrophy	+++	Hemorrhagic pancreatitis	Diffuse pancreatic necrosis	Pancreatic necrosis

At autopsy the pancreas was small and exceedingly firm on section, and the ducts were dilated throughout their course. Microscopic examination of the pancreatic parenchyma revealed a marked overgrowth of connective tissue, dividing the disrupted cell groups into lobules. The remaining acini were composed of flat epithelium which appeared vacuolated and atrophic. The islands of Langerhans were numerous and somewhat hypertrophic (fig. 12).

For the greater part, chronic pancreatitis with fatty infiltration and early degenerative changes constituted the outstanding pathologic picture. However, in 1 instance hemorrhagic pancreatitis, apparently due to the escape of active enzymes from a retention cyst following ligation of the acini, resulted from the procedure.

In this series of animals life expectancy was materially reduced and death occurred as the result of the added burden of the second stage operations or of an intercurrent infection.

CONCLUSIONS

1. By a modification of the Tripodi and Sherwin method the pancreas can be transplanted into the stomach without danger of immediate acute pancreatitis or peritonitis.

2. The transplanted pancreas retains its external and internal functions and shows no sign of atrophy.

3. Lipid deposition and degeneration of the liver do not follow pancreatic transplantation.

4. Complete exclusion of the external secretion of the pancreas by the stated methods produces an abnormal deposition of fat in the liver and concomitant degeneration and atrophy of the liver cells.

5. The presented method of conserving the pancreatic secretion offers a favorable means of approach in the radical treatment of malignant lesions involving the periampullary region and the head of the pancreas.

TRAUMATIC SUBCUTANEOUS RUPTURE OF THE NORMAL SPLEEN

LOUIS T. WRIGHT, M.D.
AND
AARON PRIGOT, M.D.
NEW YORK

This paper is based on 29 cases of subcutaneous rupture of the normal spleen, due to trauma, observed by us at the Harlem Hospital. Connors [1] reviewed the cases in which the condition was treated at the same hospital from 1905 to 1927 inclusive. One of us (L. T. W.) had the opportunity to study many of these cases. The present report covers the period from Jan. 1 to Sept. 1, 1938. It was thought advisable to review this group of cases and whenever possible to compare them with the cases reported by Connors, since the two series represent a continuous study in one institution over a period of years. Some of the tables to be presented have been included for the sake of completeness; others indicate aspects of the subject that have not been mentioned in the literature. In all cases in the series, operation or autopsy proved the spleen to be the injured organ and histologic section showed normal splenic tissue.

This condition is not as infrequent as one is led to believe by the various reports in the literature. During the period covered by this report there were approximately 20,000 patients admitted to the traumatic service of the Harlem Hospital. Thirty of these patients had rupture of the spleen. This indicates roughly an incidence of 1:666. With the continued increase in the number of automobile accidents this ratio will probably rise.

There is wide variation in general opinion as to the frequency of rupture of the spleen as a complication of intra-abdominal injuries. Mazel [2] stated that rupture of the spleen occurs in 30 per cent of subcutaneous injuries to the abdominal viscera. Bronaugh [3] stated that injury to the spleen occurs in 33.3 per cent of injuries involving abdominal organs. Angle and Kassel [4] stated the opinion that these figures are high.

From the Surgical Service of the Harlem Hospital.

1. Connors, J. F.: Ann. Surg. **88**:388, 1928.
2. Mazel, M. S.: Illinois M. J. **62**:170, 1932.
3. Bronaugh, W.: West Virginia M. J. **31**:360, 1935.
4. Angle, L. W., and Kassel, H. W.: J. Kansas M. Soc. **36**:22, 1935.

In studying the incidence of subcutaneous rupture of the spleen, liver, intestines, mesentery and pancreas one finds that splenic injury is more common than is generally believed. Data on the relative frequency of subcutaneous injuries to these structures (table 1) show that the spleen is involved in 47.6 per cent of cases of pathologic conditions of the viscera due to subcutaneous injury.

It is of interest to note that according to our experience seasonal variations are unimportant (table 2). The cases are listed according to the year and month in which the injury occurred.

TABLE 1.—*Incidence of Rupture of the Spleen*

Subcutaneous Rupture	No. of Cases	Percentage
Spleen	30	47.6
Liver	18	28.6
Intestines	11	17.5
Mesentery	3	4.7
Pancreas	1	1.6
Total number of cases	63	100.0

TABLE 2.—*Seasonal Distribution of Cases of Rupture of Spleen*

Year	No. of Cases	Month	No. of Cases
1928	2	January	2
1929	1	February	2
1930	4	March	5
1931	1	April	1
1932	3	May	2
1933	7	June	2
1934	1	July	5
1935	3	August	2
1936	1	September	4
1937	3	October	1
1938 (to September 1)	4	November	2
		December	2
Total number of cases	30	Total number of cases	30

Subcutaneous rupture of the normal spleen may be traumatic or apparently spontaneous. Many authors [5] have concluded that apparently spontaneous rupture occurs only in the diseased spleen. However, from time to time one finds reports in the literature on spontaneous rupture of the normal spleen. In our 30 cases there was but 1 of supposedly spontaneous rupture. This case was reported by Young [6] from this hospital. The spleen was normal.

5. (*a*) Smith, S.: Forensic Medicine, ed. 4, London, J. & A. Churchill, Ltd., 1934. (*b*) Ledderhose, G.: Die chirurgischen Erkrankungen der Bauchdecken und die chirurgischen Krankheiten der Milz, in Billroth, C. A. T., and Luecke, G. A.: Deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1890, no. 45b. p. 147. (*c*) Foucault, P.: J. de méd. de Bordeaux **102**:1138, 1925.

6. Young, R. H.: Ann. Surg. **101**:1389, 1935.

Trauma, then, accounts for rupture of the normal spleen in the greatest number of cases. The trauma may vary in type and severity, and the resultant injury to the spleen may not be correlated with the severity of the trauma. The force may be sudden, severe or mild and may or may not be directed against the splenic area. Not infrequently there are associated lesions.

The automobile continues to be the traumatic agent in the greatest number of cases. Table 3 shows how the nature of the trauma varies. Table 4 gives the percentages for this series and that of Connors.[1]

TABLE 3.—*Trauma in Cases of Splenic Rupture*

Trauma	Present Series (1928-1938)	Connors' Series (1905-1927)
Struck by automobile	15	18
Passengers in automobile accident	5	0
Struck by motorcycle	0	1
Falling		
Out of windows	3	1
To the ground	3	3
Down elevator shaft	0	1
From carriage seat	0	1
Into areaway	0	1
Struck by falling body of another person	0	1
Assault and battery	2	1
Run over by wagon	0	3
Undetermined	1	1
Struck by bicycle	1	0
Colliding with tree	1	0

TABLE 4.—*Percentages for Trauma in Cases of Splenic Rupture*

Trauma	Present Series (1928-1938) Percentage	Connors' Series (1905-1927) Percentage
Motor accidents	63.3	59.4
Falls	20.0	21.9
Assault and battery	3.3	3.1
Assault and battery	6.7	3.1
Run over by wagon	0.0	9.4
Undetermined	3.3	3.1
Struck by bicycle	3.3	0.0
Falling body	0.0	3.1
Colliding with tree	3.3	0.0

Correlation of the age incidence with the traumatic agent reveals some interesting and significant facts. There were 9 patients, or 30 per cent, between the ages of 5 and 10 years, inclusive. Of these, 8 were injured in automobile accidents and the ninth by a fall against the curbstone (table 5).

In the age group from 11 to 20 years inclusive there were 5 patients, or 16 per cent. The patients in this group were more capable of handling themselves in respect to automobile injuries. Only 2 were struck by automobiles. The third was injured while riding in an automobile; the fourth was struck by a bicycle, and the fifth was injured while coasting.

Alcohol played a prominent role in the injuries of patients aged from 21 to 30 inclusive (7 patients, or 23.3 per cent). Three were hurt by falling while drunk; 1 was involved in an automobile accident while inebriated; 2 were injured by automobiles, and 1 either fell or jumped from a fourth story window.

Six patients, or 20 per cent, were in the age group between 31 and 40 years, inclusive. Two were victims of assault and battery; 3 were

TABLE 5.—*Age and Sex of Patient Correlated with Type of Trauma*

Age	Sex		Total	Trauma				
	Male	Female		Automobile Accidents	Assault and Battery	Falling	Injury in Coasting	Bicycle Accident
5	2	1	3	3	..	..	..	..
6	1	..	1	1	..	..	..	..
8	3	1	4	4	..	..	..	..
10	1	..	1	..	..	1	..	..
11	1	..	1	..	..	..	..	1
12	1	..	1	1	..	..	..	..
17	..	1	1	..	..	..	1	..
20	2	..	2	2	..	..	..	..
22	..	1	1	1	..	..	..	..
23	1	..	1	..	..	1	..	..
25	1	..	1	..	..	1	..	..
26	1	..	1	..	..	1	..	..
27	1	1	2	1	..	1	..	..
28	1	..	1	1	..	..	..	..
32	1	..	1	..	1	..	..	..
36	..	1	1	1	..	..	..	..
38	1	1	2	1	1	..	..	..
39	1	..	1	..	..	1	..	..
40	1	..	1	1	..	..	..	..
42	1	..	1	1	..	..	..	..
47	1	..	1	..	..	..	..	..
61	1	..	1	1	..	..	..	..
	23	7	30	19	2	6	1	1

TABLE 6.—*Comparative Age Incidence of the Two Series*

Age, Years	This Series (1928-1938) Percentage	Connors' Series (1905-1927) Percentage
0 to 10	30.0	43.8
11 to 20	16.6	25.0
21 to 30	23.3	9.4
31 to 40	20.0	9.4
41 to 50	10.0	12.5

involved in automobile accidents, and 1 fell and injured himself while under the influence of liquor.

In the final age group (43 to 61 years, inclusive) there were 3 patients, or 10 per cent. Two were injured by automobiles, and the cause of injury to the third was undetermined.

A comparison of the age incidence in this series with that in the series reported by Connors reveals a tendency toward a relatively greater incidence in the older age groups. Traumatic subcutaneous rupture of the normal spleen still occurs most frequently in children (table 6).

In table 5 one observes that there were 7 female patients in the 30 cases, representing 23.3 per cent of the total number. (This is not essentially different from the incidence reported by Connors.[1] In his series of 32 cases there were 7 female patients, or 21.8 per cent.) Of the 7 females involved, 5 were hurt in automobile accidents; the sixth fell from a window, and the seventh was injured while coasting.

The injury in 19 of the 30 cases was caused by automobile accidents; one finds, therefore, that there were proportionately more associated lesions. When the traumatic agent was of a sort to cause milder injury, rupture of the spleen alone was not uncommon. The position was formerly held that traumatic rupture of the spleen is always accompanied

TABLE 7.—*Lesions Associated with Rupture of the Spleen*

	Associated Conditions								
Case No.	Fractured Ribs	Broken Bones	Lacerated Kidney	Ruptured Lung; Hemopneumothorax	Injury to Brain	Ruptured Diaphragm	Ruptured Bladder	Ruptured Liver	Trauma
1	1	1	1	..	..	1	..	..	Automobile accident
2	1	1	1	1	..	..	..	..	Automobile accident
3	1	..	..	..	..	..	..	..	Automobile accident (passenger)
4	1	..	1	1	1	..	..	..	Automobile accident
5	..	1	..	..	..	..	1	..	Fall
6	1	1	..	..	..	..	..	..	Automobile accident
7	1	1	..	1	..	..	..	..	Automobile accident
8	..	..	1	..	1	..	..	1	Fall
9	..	1	..	..	..	..	..	..	Automobile accident
10	..	..	..	..	..	..	..	1	Drunk ?
11	1	1	..	..	1	..	..	..	Automobile accident
12	1	..	1	..	..	..	..	..	Automobile accident
13	..	..	..	..	..	..	..	1	Automobile accident
14	..	1	..	..	..	..	..	..	Automobile accident
15	1	..	1	..	..	..	..	..	Automobile accident
16	1	..	..	..	..	..	..	..	Automobile accident (passenger)
17	..	..	..	1	..	..	..	..	Automobile accident
	10	8	6	4	3	1	1	3	

by associated lesions. The report of Connors and subsequent reports in the literature have shown that this opinion is untenable.

There were 17 cases (table 7) in which severe associated lesions were present. Of the 17 patients 12, or 70.5 per cent, were struck by automobiles and 2, or 11.8 per cent, were riding in automobiles involved in accidents. This makes a total of 14 cases (82.3 per cent) in which the injury was directly or indirectly due to the automobile accident. In 2 cases the injury was caused by falls from a considerable height. In the last case there was no history of trauma, but we have every reason to believe that the patient was injured while under the influence of liquor.

The frequency of the various associated lesions, in the order of their occurrence, is given in table 8. There were 10 cases in which the injury was associated with fractured ribs; in 9 of these the lower ribs

of the left side were involved. The frequency of fractured ribs on this side was first noted by Chalier.[7]

Because of the frequency of associated lesions causing diagnostic difficulties in our series of cases, we shall (except in 1 or 2 instances) base our classification of traumatic rupture of the normal spleen on the cases in which no complication was present.

There is considerable variation in the clinical manifestations of splenic rupture, due to the character of the internal concealed hemorrhages which dominate the symptoms; classification, therefore, is not easy. It is clear that any classification must be somewhat elastic.

Mazel [2] divided the cases into the following groups:

1. Cases of immediate hemorrhage. The hemorrhage may be so copious as to cause sudden collapse and death before any steps can be taken.

2. Cases of less severe hemorrhage. A moderate hemorrhage develops, and all the signs of internal hemorrhage are present.

TABLE 8.—*Complications in Order of Frequency*

Associated Lesions	No. of Cases
Fractured ribs	10
Broken bones (simple or compound fractures)	8
Lacerated kidney	6
Hemothorax, pneumothorax, lacerated lung	4
Cerebral complications, fractured skull, lacerated brain	3
Ruptured liver	3
Ruptured urinary bladder	1
Ruptured diaphragm	1

3. Cases of delayed hemorrhage. The signs of internal hemorrhage are not obvious for days or weeks.

In our opinion there are five distinct clinical types, dependent on the rate of hemorrhage:

1. Massive hemorrhage, causing almost immediate or sudden death.

2. Acute hemorrhage, producing shortly after the injury a state of shock which rapidly becomes deeper.

3. Repeated small hemorrhages. The patients enter the hospital in good condition but show signs of slow progressive hemorrhage—increasing anemia, a rising pulse rate, a fall in blood pressure and progressive weakness.

4. Late hemorrhage. The patients have an initial injury from which they recover. After a period of relief from symptoms they may suddenly go into shock, showing signs of acute internal concealed hemorrhage, or they may have a recurrence of signs and symptoms of repeated small hemorrhages. They may gradually become worse, showing signs of increased hemorrhage over a period of days or weeks.

7. Chalier, A.: Lyon chir. **24**:69, 1927.

5. Spontaneous cure. The patients show no signs of hemorrhage and suffer only localized pain, which soon disappears.

In this series there were no cases of massive hemorrhage, although such cases have been reported in the literature.[8] The pathologic condition consists of severe lacerations of the spleen. Parts of the organ may be found lying free in the abdominal cavity. The vessels in the hilus or the pedicle are usually torn. Tears involving the hilus or the pedicle do not necessarily cause death, as is illustrated by Armitage's [9] case. A badly fragmented spleen sometimes may cause only symptoms of acute or delayed hemorrhage.

In the group in which acute hemorrhage occurs, the patients, although brought to the hospital shortly after the accident, are in shock on admission. The condition of the patient becomes worse as the shock becomes deeper. This is illustrated by the following case.

CASE 18.—On July 12, 1930, a boy aged 5 years was brought to the hospital complaining of pain in the back and abdomen. One hour before admission the patient was said to have been struck by an automobile. At no time, however, was he unconscious. Physical examination revealed him to be in shock. The pulse rate was 116. The temperature was 101 F. There was a tender mass in the left upper abdominal quadrant. The urine was normal. A diagnosis of rupture of the spleen was made, and splenectomy was done. The boy made an uneventful recovery. The condition in this case was typical of the group. The spleen was severely lacerated, and in some regions the tear involved the hilus.

Renton [10] described a similar case. Mulloy [11] also reported a similar case in which a fragment of spleen was found lying free over the bladder. The patients in both cases were adults.

In cases of "repeated small hemorrhage," after the initial injury the patient's condition gradually becomes worse, with obscure abdominal symptoms and progressive weakness until shock intervenes or until the internal concealed hemorrhage becomes evident and surgical intervention is begun. Ten of our 14 cases in which no complication was present belong in this group. Eight of the patients were males and 2 were females. Their ages varied from 8 to 50 years. Case 19 is typical of this group. The pathologic condition is variable. The spleen may or may not be enlarged by a subcapsular hemorrhage. The capsule may show one or more rents scattered over the surface of the spleen. These lacerations involve the splenic parenchyma, vary from 2.5 to 7.5 cm. in length and may contain blood clot. The splenic capsule may not rupture, but there may be a subcapsular hematoma, which increases in size.

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8. (*a*) Berger, E.: Arch. f. klin. Chir. **68**:768, 1902. (*b*) Bailey, H.: Brit. J. Surg. **17**:417, 1930.

9. Armitage, G.: Brit. J. Surg. **17**:335, 1929.

10. Renton, M. W.: Brit. M. J. **2**:470, 1934.

11. Mulloy, J. P.: Canad. M. A. J. **34**:680, 1936.

CASE 19.—A 39 year old man was admitted to the hospital on July 8, 1933 because of vomiting and abdominal pain of one day's duration. On the day before admission, while sitting on a park bench, the patient vomited food. The vomitus contained no gross blood. Immediately afterward he experienced severe sharp sticking periumbilical pain. The pain persisted but began to radiate to the left side of the back and to the left shoulder. On coughing the pain radiated also to the right shoulder. Since the onset of the attack, he had become progressively weaker and short of breath. He had several watery stools containing fresh blood. On the night before admission he had three chills. He had been "on a drinking spree" for three months prior to admission.

There had been a stab wound of the abdomen twenty-five years previously and lobar pneumonia one year prior to admission. During the past year he had been treated for "stomach trouble" with powders and he was placed on a diet for convalescent patients with gastric ulcers. No roentgenograms were taken at this time.

Physical examination revealed him to be well nourished and well developed. He was dyspneic, cyanotic and acutely ill. There was dulness at the base of the right lung. The pulse rate was 110, the respiratory rate 30, the temperature 100 F. and the blood pressure 120 systolic and 82 diastolic. The abdomen was distended and tender throughout.

The urine was normal. The value for hemoglobin was 70 per cent. The erythrocyte count was 4,400,000 and the leukocyte count 13,850 per cubic millimeter.

After a clysis the patient began to show signs of improvement. A roentgenogram of the abdomen showed no free air under the diaphragm. An abdominal tap gave negative results. A diagnosis of acute abdominal disease was made. It was decided to observe the patient for a short period. The next morning, twenty hours after admission, the pulse rate rose to 120 and the temperature to 102.8 F. The abdominal distention increased. The patient finally went into shock. Operation and transfusion were then done. At operation a ruptured spleen was found. The patient died one-half hour after the operation.

There is a group of cases in which late hemorrhage takes place and in which there is a period of symptomatic relief, termed by Baudet[12] "the latent period." The asymptomatic period is terminated by some minor incident, such as straining at stool or muscular spasm, or even for no apparent reason. Contrary to general opinion, the second hemorrhage may not begin dramatically with acute symptoms of loss of blood but may have an insidious onset.

There were 2 cases of late hemorrhage. Both patients were women, aged 22 and 36 respectively. McIndoe[13] has collected 46 similar cases, in which the ages of the patients varied from 8 to 63 years. Only 4 of the patients were females. Other cases have been reported in the literature.[14]

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12. Baudet, R.: Méd. prat. **3**:565, 1907.

13. McIndoe, A. H.: Brit. J. Surg. **20**:249, 1932; Proc. Staff Meet., Mayo Clin. **3**:365, 1928.

14. Wenger, L.: Brit. M. J. **1**:1235, 1936. Gardner, R.: ibid. **1**:416, 1935. Wilson, F.: Lancet **1**:1236, 1927. Ryan, C. E.: Wisconsin M. J. **32**:523, 1933. Cellan-Jones, C. J.: Brit. M. J. **2**:700, 1928. Livingston, J.: ibid. **2**:16, 1930. Dawson-Walker, E. F.: Lancet **1**:523, 1931. McIndoe.[13]

CASE 20.—A 36 year old woman was admitted to the hospital on March 12, 1937, complaining of pain in the left side of the chest and the left shoulder. Two weeks previously she had been in an automobile accident and had been unconscious for a short time, but had recovered in a few days. At that time she had had some tenderness in the left upper quadrant of the abdomen, which had disappeared. On the day of admission, while sitting in a theater, she suddenly had a sharp pain in the left side of the chest and fainted. She regained consciousness but noticed that she was short of breath and that the pain was radiating to the left shoulder. She was nauseated but did not vomit. Her past history was irrelevant except for an oophorectomy five years before admission. Physical examination revealed her to be acutely ill. The temperature and the pulse rate were normal. The blood pressure was 90 systolic and 74 diastolic. There were tenderness and rigidity in the left upper abdominal quadrant. The urine was normal. The value for hemoglobin was 65 per cent. The erythrocyte count was 2,900,000 and the leukocyte count 6,100 per cubic millimeter. The abdomen was tapped, and blood was revealed in the left upper quadrant. This confirmed the diagnosis of intra-abdominal hemorrhage.

A diagnosis of acute pancreatitis was accordingly made. At operation a ruptured spleen was found. After a splenectomy and transfusion the patient made an uneventful recovery.

CASE 16.—This case is interesting because of the fact that the asymptomatic period was broken by a recurrence of symptoms. On June 25, 1938, a woman aged 22 was admitted to the hospital complaining of pain in the left side of the chest, radiating to the left shoulder, of one day's duration. Three weeks previously the patient had been involved in an automobile accident, sustaining a fracture of the eighth rib on the left. However, she was completely asymptomatic three days after the accident. One week before admission she began to have pain in the left side of the chest and general malaise. Three days later she again became asymptomatic and remained so until the onset of the present illness. Physical examination revealed that she was not acutely ill. The temperature, pulse rate and respiratory rate were normal. There was dulness at the base of the left lung, with bronchial breathing over it. The abdomen showed tenderness and spasm in the left upper quadrant. A roentgenogram of the chest revealed a high diaphragm on the left side and a fracture of the left eighth rib. The urine was normal. The value for hemoglobin was 45 per cent. The erythrocyte count was 2,700,000 and the leukocyte count 21,300 per cubic millimeter. Because of the findings in the chest a diagnosis of pneumonia was made. A thoracic tap revealed bloody fluid. The abdominal symptoms became more pronounced. A diagnosis of rupture of the spleen was made. Laparotomy confirmed this diagnosis. The patient recovered after a splenectomy.

The pathologic changes in cases of this type consist of (1) minor superficial capsular rupture with ecchymosis and slow hemorrhage, (2) intrasplenic hematoma and subcapsular hemorrhage with subsequent capsular rupture and (3) capsular and parenchymal rupture with an encapsulated perisplenic hematoma. Frequently the surrounding organs, especially the omentum, tend to wall off the lesion.

Of the final group of cases, in which "spontaneous cure" occurs, we know of no instances in this hospital. In 3,000 autopsies our pathologist has seen no evidence of traumatic cysts of the spleen, although such

cysts have been reported.[15] Instances of spontaneous cure have been noted. A case reported by Hunter[16] in which operation was performed proves that this may take place. Gordon-Watson[17] described 2 spleens, 1 of which belonged to a woman aged 30 who fell 9.14 meters and fractured her femur. Autopsy, performed ten days after the accident, revealed that the spleen was torn across but that there was a firm scar between the lacerated surfaces. The other specimen was removed post mortem from a woman aged 30 who had been run over by an automobile and had died sixty hours after the accident. A rent in the spleen was closed by a firm clot. Had these 2 patients lived, their cases might have fallen into the group in which late hemorrhage is the distinguishing feature.

The diagnosis of subcutaneous rupture of the normal spleen is not easy. There are no signs or symptoms pathognomonic of this condition; one must, therefore, consider each case on its own merit. The symptoms and signs of rupture of the spleen are chiefly those of local injury and those of hemorrhage, shock and peritoneal and diaphragmatic irritation.

Abdominal pain is the most common complaint. This pain is usually sharp and lancinating and is localized in the left upper quadrant. However, it may be described as generalized abdominal soreness and is sometimes more acute in the other quadrants. All the patients either entered with this symptom or had it while under observation.

The radiation of this pain to the left shoulder (Kehr's sign[18]) is not uncommon. It occurred in 3 cases. In 1 case the pain radiated to the right shoulder when the patient coughed. Pain in the left shoulder also occurs in association with other conditions in which there is irritation of the diaphragm. The presence of Kehr's sign is not dependent on the quantity of blood in the abdominal cavity. In the case in our series in which the most blood was observed in the abdominal cavity this sign did not appear.

Pain in the chest occurred in 12 cases but was associated with fractured ribs on the left side in 9. In the other 3 it was localized to the left side and was not increased by respiration or coughing.

The symptom next in order of frequency is dyspnea. Eight of our patients complained of being "short winded" or had some form of respiratory distress. This distress may be due to diaphragmatic irritation, injury to the chest wall or acute loss of blood.

15. Novak, E.: Surg., Gynec. & Obst. **45**:586, 1927. Starr, F. N. G.: Ann. Surg. **98**:919, 1933.

16. Hunter, E. A.: Brit. M. J. **2**:256, 1935.

17. Gordon-Watson, in Choyce, C. C.: A System of Surgery, ed. 2, London, Cassell & Co., 1923, vol. 2, p. 114.

18. Kehr, cited by DaCosta, J. C.: Modern Surgery, General and Operative, ed. 10, Philadelphia, W. B. Saunders Company, 1931, p. 984.

Vomiting occurred in 3 cases and diarrhea in 2. The patients in whose cases we observed vomiting and diarrhea had been drinking alcoholic liquors prior to admission, so that these symptoms may have been related not to the splenic injury but to gastroenteritis.

The physical findings are more helpful. In all cases there were abdominal tenderness and spasm. The point of maximum tenderness was not necessarily localized to the splenic area. The results of abdominal examination were further obscured by the fact that the trauma which produces the splenic injury may cause contusion of the abdominal wall. More important is the fact that in no case were there any external marks on either the abdomen or the back.

Table 9 gives the location of the region of tenderness and spasm in our cases.

During the past few years we have been looking for an instance of a positive Cullen sign.[19] As yet none has been noted.

Shifting dulness and Ballance's [20] sign were noted in only 6 cases. Abdominal distention, usually soft, occurred in 6 cases.

TABLE 9.—*Localization of Abdominal Tenderness and Spasm*

Region	Number of Cases
Left upper quadrant	14
Generalized	6
Both upper quadrants	5
Periumbilical	1
Both lower quadrants	2
Right side	2

An abdominal mass in the left upper quadrant was noted in 1 case.

In another case a flat roentgenogram of the abdomen showed a dense shadow under the left leaf of the diaphragm.

Three patients fainted prior to admission. They quickly regained consciousness. Seven patients were brought to the hospital unconscious and in deep shock. All of these had severe associated lesions. All patients regained consciousness while under observation.

The temperature on admission varied from subnormal to 103 F. In general, patients who had severe associated lesions and who were admitted unconscious or in shock tended to have either a subnormal or a normal temperature.

The circulatory system showed wide variations. Patients admitted in shock showed a rapid, thready pulse, low blood pressure and low pulse pressure. Of the 17 patients with associated lesions only 3 showed a normal blood pressure and pulse rate. Of the patients with-

19. Cullen, T. S., in Contributions to Medical and Biological Research, Dedicated to Sir William Osler, New York, Paul B. Hoeber, Inc., 1919, p. 420.

20. Pitts, B., and Ballance, C. A.: Tr. Clin. Soc. London **29**:77, 1896; Lancet **1**:485, 1896.

out associated lesions only 1 entered with a low blood pressure and pulse rate. In general the pulse rate varied between 100 and 140 and the blood pressure from normal to 64 systolic and 40 diastolic. The diagnosis of internal hemorrhage in the case of a patient admitted to the hospital in shock is extremely difficult, and a careful observation of the change in blood pressure and the increase in pulse rate will soon impress the observer, so that adequate measures may be taken.

Examination of the cellular elements and the hemoglobin content of the blood is important. The erythrocyte count and the value for hemoglobin may be normal, but in all except 1 case in our series the latter was low, ranging from 40 to 80 per cent. In the case in which the value for hemoglobin and the red blood cell count were normal the patient was in shock. In all the other cases the red blood cell count ranged from 2,400,000 to 4,400,000 per cubic millimeter. More important is the change noted in the number of red blood cells after repeated determinations. The white cell count ranged from 6,000 to 23,850 per cubic millimeter and not infrequently failed to rise with increasing temperatures.

The urine was normal in all but 7 cases. In these 7 cases it contained blood, and splenic rupture in these cases was associated with laceration of the kidney or bladder. However, one should not be content with a diagnosis of ruptured kidney merely because the urine is pathologic, but should look for evidence of concealed hemorrhage.

There are certain diagnostic procedures which facilitate the diagnosis of rupture of the spleen. Burke and Madigan [21] reported a case of ruptured spleen in which the patient was given colloidal thorium dioxide. They concluded that thorium dioxide is of practical use in the diagnosis of traumatism of the liver and spleen when physical signs are observed. They claimed that this substance has no deleterious effects even when given intravenously. Damage to the liver and spleen does not contraindicate its use. A dose smaller by half than the usual dose will give satisfactory results in four hours. We do not endorse this procedure, because it is both slow and dangerous.

In our hands the abdominal tap has proved to be of invaluable aid in the diagnosis of subcutaneous injury of the abdominal viscera. In fact, we feel that it is inexcusable to neglect to make an abdominal tap in all cases in which intra-abdominal complications are suspected. This is especially true in cases in which severe associated lesions mask the abdominal complications. In 15 cases of rupture of the spleen the abdominal tap was employed; it gave positive results in 13. It was employed in 1 case of subcapsular rupture of the spleen, and in this case it gave negative results.

21. Burke, W., and Madigan, J.: Radiology **21**:580, 1933.

We have ample evidence to show that the finding of blood by abdominal tap is indicative of intra-abdominal injury. In 3 cases of contusion of the abdominal wall the abdomen was tapped and no blood was obtained. In 1 of these cases there were subsequently normal findings. In the second case postmortem examination showed no intra-abdominal injury.

We have had 3 cases of "false positive" results, in 2 of which there were ruptured kidneys. In both these cases exploration revealed a large retroperitoneal hematoma. In the third case there were signs of concealed hemorrhage. In this case (case 21) autopsy showed bleeding into the mediastinum.

In the cases of 2 patients with rupture of the spleen, the results of the abdominal tap were negative. One case (case 19) has been reported. The other is given in detail below.

CASE 8.—A 25 year old man was admitted to the hospital on Oct. 29, 1933, after an accident in which he fell from a window. He was conscious but not rational. Physical examination revealed him to be well developed and well nourished. The pulse rate was 70, the respiratory rate 20 and the blood pressure 116 systolic and 90 diastolic. There was no bleeding from the nose and mouth. The remainder of the examination gave normal results. The urine showed albumin and red blood cells. The value for hemoglobin was 75 per cent. The erythrocyte count was 4,000,000 and the leukocyte count 7,900 per cubic millimeter. On admission, a spinal tap revealed a bloody fluid. On the day after admission tenderness in both costovertebral angles was found. A roentgenogram of the chest suggested pneumothorax on the right side. The pulse, which up to this time had been normal, began to rise, reaching 120, and the blood pressure fell to 94 systolic and 60 diastolic. An abdominal tap was reported to give negative results. Because of the hematuria and the bilateral tenderness in both costovertebral angles a diagnosis of laceration of the kidneys was made. On the fourth day after admission the patient began to have abdominal pain and dyspnea and died suddenly. Postmortem examination revealed ruptures of the liver, kidneys, spleen and diaphragm. There were a subarachnoid hemorrhage and hemothorax. The abdominal cavity contained about 500 cc. of blood.

From our experience in these cases we have learned that if an abdominal tap gives negative results and the patient continues to show signs of concealed hemorrhage the tap should be repeated.

Our experience with the abdominal tap has been satisfactory, and we do not hesitate to use it. It is especially helpful in cases in which the diagnosis is obscure, in cases in which the patient is admitted unconscious and in shock and in cases in which the physical findings are obscured either by fractured ribs or by concealed hemorrhage into cavities of the body other than the peritoneal.

The diagnosis of subcutaneous rupture of the spleen is not an easy one to make. When the history of trauma bears a direct relation to the chain of symptoms of acute abdominal pain and weakness and to the finding of abdominal tenderness and spasm with a rapid pulse and low blood pressure, a presumptive diagnosis of rupture of the spleen

may be made. The laboratory findings may or may not show evidence of acute loss of blood. Although Kehr's, Ballance's and Cullen's signs are helpful when present, their absence is of no significance.

There are many conditions which may obscure the diagnosis of rupture of the spleen. Contusion of the abdominal wall gives a picture similar to that of subcutaneous splenic rupture; however, in cases of contusion the pulse rate, blood pressure and blood cells are generally normal.

Fracture of the lower ribs on the left side with shock gives a clinical picture identical with that associated with rupture of the spleen. Not infrequently fracture of these ribs is associated with rupture of the spleen. In such a case the finding of blood in the peritoneal cavity and tapping the abdomen are of great importance.

The abdominal tap also aids in localization of the concealed hemorrhage. A patient with abdominal signs and symptoms and evidence of acute loss of blood may be bleeding into cavities other than the peritoneal.

The following case proved not to be an instance of rupture of the spleen, although this diagnosis was made preoperatively. An exploratory laparotomy was performed because blood was obtained on abdominal tap. The case shows how careful one must be not to make a mistake.

ILLUSTRATIVE CASE.—A 60 year old man was admitted to the hospital on Sept. 22, 1938. He was said to have fallen down a flight of stairs. On admission he appeared acutely ill and was confused and drowsy. The temperature was 99.2 F. The pulse rate was 100, and the quality of the pulse was fair. The blood pressure was 96 systolic and 78 diastolic. There was a small laceration of the scalp. There was generalized rigidity of the abdomen, with tenderness to pressure in the epigastrium. The value for hemoglobin was 60 per cent. The erythrocyte count was 3,500,000 and the leukocyte count 8,600 per cubic millimeter. The urine was normal. An abdominal tap revealed blood. A tentative diagnosis of rupture of the spleen or of the liver was made, but after the patient had been in the hospital for two hours he began to improve mentally. However, subcutaneous emphysema developed over the left side of the thoracic wall. The pneumothorax reading was —2. At this time it was found that there was a fracture of the eighth, ninth and tenth ribs on the left in the midaxillary line. Underwater drainage was instituted for tension pneumothorax. Because of the positive results of an abdominal tap, an exploratory laparotomy was done with the region under local anesthesia, but no intra-abdominal lesion was found. The patient died nine hours after the operation. Postmortem examination revealed multiple fractures of the ribs, laceration of the lung and multiple contusions of the thoracic wall and of the lung.

An exact diagnosis cannot be made except on the basis of probability. As we have shown that the spleen is involved in 50 per cent of cases of intra-abdominal complications, the most likely diagnosis is that of rupture of the spleen. However, we have been misled, as the following case will show.

ILLUSTRATIVE CASE.—A 12 year old boy was brought to the hospital on Sept. 9, 1938, complaining of generalized abdominal pain. Shortly before admission he had been struck by an automobile. He was unconscious. On admission he was cooperative and complained of pain and shortness of breath. The past history, except for the usual diseases of childhood, was irrelevant. Physical examination revealed the boy to be well developed and well nourished. The temperature was 99 F., the pulse rate 110, the respiratory rate 30 and the blood pressure 130 systolic and 80 diastolic. Tenderness and rigidity were present in both upper quadrants of the abdomen. The urine was normal. The value for hemoglobin was 70 per cent. The red blood cell count was 3,800,000 per cubic millimeter. While under observation the patient seemed to become more anemic and the pulse rate began to rise. Abdominal tap showed blood in the left upper quadrant. Operation revealed a laceration on the posterior surface of the right lobe of the liver. This rent was packed. The patient was given a slow drip transfusion. He made an uneventful recovery and was discharged on October 2.

Rupture of the spleen is an acute abdominal emergency, and as such has to be differentiated not only from other intra-abdominal lesions but from lesions involving concealed hemorrhage into other cavities of the body. A study of the cases in which we have missed the diagnosis will bring out the complexity of this problem.

The diagnosis was missed in 7 of our 30 cases. It seems desirable, therefore, to include table 10, in which are listed the cases in which a mistaken diagnosis was made. Perforated peptic ulcer was the most common erroneous diagnosis, probably owing to the fact that no history of trauma was obtained. In 2 cases the history of trauma was not readily linked with the subsequent chain of events; in 1 case, therefore, a diagnosis of acute hemorrhagic pancreatitis was made, and in another, because of the thoracic findings, the diagnosis was that of pneumonia. The diagnosis is most frequently missed when the history of trauma is not obtained or, if obtained, is disregarded because the possibility of late hemorrhage is not kept in mind. Other cases have been reported in which the preoperative diagnosis was acute appendicitis,[22] ruptured ectopic pregnancy (Rugnave [23]) or cholecystitis.[24] Splenic rupture may also simulate rupture of the left kidney, of the liver or of a gastric ulcer.[25]

Finally, associated lesions may obscure the signs and symptoms of intra-abdominal hemorrhage. In 1 case we were satisfied with a diagnosis of laceration of the kidney because no blood was obtained on abdominal tap. In another case the abdominal findings were masked by fractured ribs on the left side. The positive results of an abdominal

22. Thomas, G. B.: Brit. M. J. **2**:1100, 1935.

23. Rugnave, cited by Stretton, J. L.: Brit. M. J. **1**:901, 1926. Wohlgemuth, K.: Berl. klin. Wchnschr. **2**:734, 1921.

24. Wallace, H. K.: J. Missouri M. A. **21**:18, 1924.

25. Heineck, A. P.: Illinois M. J. **56**: 205, 1929.

tap were disregarded, as in case 1. Bleeding not only from other types of intra-abdominal lesions but into other cavities of the body may complicate the diagnosis.

In conclusion, we may say that the diagnosis of subcutaneous rupture of the normal spleen is difficult because there is considerable variation in the clinical manifestation of this condition, owing to the character of the internal concealed hemorrhage which dominates the symptoms. The diagnosis is missed most frequently when no history of trauma is obtained or, if obtained, is disregarded because the possibility of late hemorrhage is not kept in mind. Other conditions, such as laceration of the left kidney, fractured ribs or traumatic pleurisy, may mask the presence of a ruptured spleen. The abdominal tap is of invaluable aid in the diagnosis of this condition, and when the results are negative it should be repeated if conditions warrant it.

TABLE 10.—*Diagnosis of Splenic Rupture*

Case Number	History of Trauma	Diagnosis on Admission	Preoperative Diagnosis	Result
16	Yes	Pneumonia.....	Ruptured spleen	Recovered
19	No	Perforated peptic ulcer.....	Same	Died
10	No	Perforated peptic ulcer.....	Same	Recovered
23	No	Perforated peptic ulcer.....	Same	Recovered
8	Yes	Ruptured kidney.....	.....	Died
1	Yes	Compound fracture of left tibia, fibula and humerus; fracture of left lower ribs.....	.....	Died
20	Yes	Acute hemorrhagic pancreatitis.....	Same	Recovered

The treatment of traumatic rupture of the spleen is surgical. Berger [8a] has shown that conservative treatment is fatal in 93 per cent of cases. Operative intervention, therefore, is imperative, and any delay may tend to increase the operative risk.

The preoperative treatment of this condition is directed to the establishment of an accurate diagnosis and the preparation of the patient for operation. The treatment, to be sure, must be different in individual cases. However, no patient suspected of having a ruptured spleen is given a preoperative enema. The clot formed in a bleeding spleen is friable and may be dislodged easily. Straining at stool may tend to cause a more vigorous hemorrhage.

If shock is present, it is treated in the usual manner. From our experience with other acute abdominal conditions, we have learned that if a slow drip blood transfusion is started as soon as the diagnosis is established the patient will be in a better condition to undergo the surgical procedure. This treatment is more justified because in all cases either transfusion or autotransfusion was done at operation or postoperatively. The "blood bank" has been of considerable aid in these emergencies.

There are two schools of thought concerning the time at which operation should be performed. Connors [1] stated: "Immediate operation should be performed regardless of patient's condition and splenectomy is the operation of choice." With this opinion we agree. Armitage [9] and McIndoe,[13] on the other hand, have stated the opinion that steps should be taken to combat shock, for "to operate on a patient suffering with systematic shock is unpardonable." One must remember that to delay an operation in order to pour blood into a person who is having a severe intra-abdominal hemorrhage may gain little and may delay operation to such a point that no operative procedure can be carried out. We feel that splenectomy should be done as soon as the diagnosis is made, although supportive measures, such as a slow drip transfusion and intravenous administration of fluid, are invaluable and should be begun simultaneously.

The operation of choice is splenectomy, although splenorrhaphy or tamponade or a combination of both has been done. The latter procedures, however, should be discarded in favor of splenectomy.

Tamponade is uncertain, and the bleeding may not be adequately controlled. The abdominal wound in such cases is usually weak. Berger's [26] statistics include data on 10 cases in which this procedure was used, with 1 death. Quenu [27] reported 15 cases, with 2 deaths.

Splenorrhaphy, first done by Lamarchia [28] in 1896, is not advisable, because the spleen is composed of friable tissue and is located in a region not readily accessible. The suture line may be reenforced with omentum as advocated by Gourrin.[29] This procedure has been reported to have a mortality ranging from 25 to 50 per cent. Lotsch [30] reported a 37.7 per cent mortality.

Splenectomy, the operation of choice, was first done by Roddick. The first successful splenectomy for traumatic splenic rupture was done by Rieweues [31] in 1892. The pancreas should be avoided, for injury to this organ may result in formation of a pancreatic fistula or may cause digestion of the edges of the wound with eventual evisceration. We advise splenectomy in cases in which there is subcapsular hemorrhage without rupture of the capsule. Although such lesions may resolve, the danger of subsequent rupture is great. The following case represents our experience with this condition.

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26. Berger, E.: Arch. f. klin. Chir. **68**:863, 1902.

27. Quenu, J.: J. de chir. **28**:393, 1926.

28. Lamarchia, cited by DaCosta, J. C.: Modern Surgery, Philadelphia, W. B. Saunders Company, 1931, p. 985.

29. Gourrin, V.: Des hernies traumatiques de la rate, Thesis, Bordeaux, no. 83, 1911.

30. Lotsch: Deutsche Ztschr. f. Chir. **93**:90, 1908.

31. Rieweues, cited by Bier, A.; Braun, H., and Kümmell, H.: Chirurgische Operationslehre, Leipzig, Johann Ambrosius Barth, 1912-1913.

CASE 24.—A 6 year old boy was struck by an automobile half an hour before admission to the hospital, on Dec. 7, 1935. He was not unconscious and complained of abdominal pain. Physical examination gave negative results except for tenderness in the left lower quadrant of the abdomen. The temperature was 97.6 F., the pulse rate 80 and the respiratory rate 24. The urine was normal. The erythrocyte count was 4,000,000 and the leukocyte count 23,600 per cubic millimeter. The value for hemoglobin was 80 per cent. The erythrocyte count fell to 3,400,000 and the value for hemoglobin to 50 per cent while the patient was under observation. On admission, rupture of viscera was suspected. An abdominal and a spinal tap gave negative results. Roentgenograms of the knee and ribs were normal. A roentgenogram of the chest showed broadening of the shadow of the left side of the diaphragm, suggesting the possibility of subphrenic injury. Because of evidence of concealed hemorrhage, operation was deemed advisable. Operation showed the spleen to be enlarged but not lacerated, and there was a small amount of blood in the abdomen. The wound was closed. Twenty-four hours later the patient died. Prior to death the pulse became rapid and thready. Postmortem examination revealed a laceration of the capsule of the spleen 6.2 cm. long and 0.64 cm. wide across the hilus.

The prognosis for this condition depends not only on the severity of the rupture but on the associated lesions. In the present series of 30 cases, 13 patients died. The gross mortality was 43.3 per cent.

Although every effort should be made to organize a surgical service for rapid diagnosis, it requires about two hours on the average to make a diagnosis of rupture of the spleen. Patients who die within two hours after first being seen by a physician may be considered to have been beyond operative help. We had 5 such patients. In only 83.5 per cent of cases, therefore, could the condition be classed as operable. We know that this is an arbitrary division, but it is the least open to attack, for the severity of splenic laceration or of the associated lesions leaves too much to the personal equation to be satisfactory as a criterion of operability. As long as a positive diagnosis could be made, any of our patients who were operated on were considered suitable, no matter how desperate their condition Twenty-three operations were performed, 22 splenectomies and 1 exploratory laparotomy. Six of the patients died, a gross operative mortality of 27.3 per cent. Only 5 splenectomized patients died. The operative mortality for splenectomy for traumatic rupture of the spleen in our series was 22.7 per cent. This figure compares favorably with the results reported in the literature. However, we hope to reduce the mortality by a more rapid diagnosis with the freer use of the abdominal tap, the establishment of the "blood bank" and the maintenance of proper water balance.

Table 12 summarizes the 7 cases in which the patients died without operation. In 2 of the cases the diagnosis was missed, although in 1 of these there was evidence of intra-abdominal hemorrhage. This evidence was disregarded. Both patients had severe associated lesions but did not receive the attention they deserved. Five patients were

moribund on admission and died within two hours. The diagnosis of intra-abdominal complications was made, but not in time to be of benefit to the patient. In 1 case (case 24) there was a subcapsular hematoma. Exploratory laparotomy was done and the spleen left in situ. The spleen later ruptured. Because of this experience we feel that splenectomy should be done in all cases of traumatic splenic damage.

TABLE 11.—*Comparative Mortality of Splenectomy for Traumatic Rupture of the Spleen*

Author	Number of Splenectomies	Mortality Percentage
McIndoe	37	27.0
Hagen	37	45.9
Lotsch	138	37.7
Planson	140	37.1
Johnson	113	30.9
Connors	25	40.0
Present series	22	22.7

TABLE 12.—*Summary of Seven Cases in Which Death Occurred*

Case No.	Associated Lesions	Time in Hospital	Diagnosis
11	Compound fracture of left tibia and fibula; fracture of left humerus; left ribs; and pelvis; cerebral concussion; shock	2 hr.	Made
15	Fractured left ribs; shock	½ hr.	Made
14	Shock; fractured humerus	2 hr.	Made
13	Shock; lacerated liver	1 hr.	Made
4	Crushed chest; lacerated lung and kidney; hemothorax; hemorrhage into galea	1 hr.	Made
1	Compound fracture of left tibia and fibula; fracture of left humerus; fracture of left lower ribs; shock; lacerated diaphragm; lacerated left kidney	6 hr.	Missed
8	Lacerated kidney and liver; hemothorax; subarachnoid hemorrhage	4 days	Missed

TABLE 13.—*Causes of Death*

Case No.	Diagnosis	Associated Lesions	Time Before Operation	Cause of Death
19	Missed	None	24 hr.	Shock
2	Made	Fracture of left tibia; left humerus and ribs; lacerated lung and kidney; shock	24 hr.	Shock
3	Made	Fractured ribs	6 hr.	Peritonitis
17	Made	Hemopneumothorax; mediastinal shift	2 hr.	Pulmonary hemorrhage
5	Made	Compound fracture of right humerus; shock; ruptured bladder	2 hr.	Shock

Twenty-two splenectomies were done; 5 of the patients died. In table 13 are outlined the causes of death.

In the first case the diagnosis was missed. This case (case 19) has been reported. The patient in case 2 had severe associated lesions and died in shock. The patient in case 3 died of peritonitis on the eighth postoperative day. Postmortem examination revealed generalized

peritonitis, thrombosis of the splenic vein, the portal vein and the pulmonary artery and lobar pneumonia. The death in case 17 was due to an oversight. The diagnosis was made, but a roentgenogram of the chest, taken preoperatively, was reported as normal. However, review of the roentgenogram showed a mediastinal shift and hemopneumothorax. The patient had general anesthesia and died at the conclusion of the operation from a pulmonary hemorrhage. In case 5 not only a splenectomy but a cystostomy was performed. The condition of this patient was very poor, and the two major surgical procedures were more than she could stand.

It will be noted that all but 1 of these patients had associated lesions and were operated on within a reasonable time after admission. The only exception was the patient in whose case the diagnosis was missed. The postoperative complications are enumerated in table 14.

TABLE 14.—*Postoperative Complications*

Case No.	Peritonitis	Pulmonary Complications	Pleuritic Reactions	Infection of Wound	Rupture of Wound
16	..	..	1	..	..
10	..	1	..	1	..
12	..	..	1	..	..
6	..	1	..	..	1
7	..	..	1	..	..
9	..	..	..	1	..
3	1	1	..	..	..
23	..	..	..	1	..
26	..	..	1	1	..

In summation, 1 patient had postoperative peritonitis and pneumonia, from which he died. Four patients had traumatic pleurisy at the base of the left lung; in the case of 1 of these the pleurisy was evident before operation. Four patients had infected wounds, while only 1 suffered a rupture of the wound. Connors [1] and Bailey [32] drew attention to disruption of the wound as being possibly due to trauma to the pancreas. Cases, however, have been reported in which the pancreas was injured at operation without subsequent infection of the wound. Peritonitis following splenectomy was believed not to occur.[33] However, this complication is always possible when the peritoneal cavity is opened.

Splenectomy has been shown to have no ill effect on the organism. This may be due to (1) assumption of the functions of the spleen by the reticuloendothelial system; (2) hypertrophy of accessory spleens or (3) splenic implants.

The spleen is a part of the reticuloendothelial system, and it is only natural that in its absence the remainder of the system assumes its functions.

32. Bailey, H.: Brit. J. Surg. **15**:40, 1928.

33. Hubbard, C. C.: New York M. J. **30**:75, 1879. Ledderhouse.[5b]

Accessory spleens are more common than is believed. Curtis and White [34] concluded that accessory spleens occur in 10 per cent of cases in which autopsy is performed. In the course of 35 splenectomies they observed accessory spleens in 7 instances. Morrison, Lederer and Fradkin [35] found that in 35 per cent of autopsies accessory spleens were observed. They also showed that such organs are most common in infancy and tend to disappear with age. Enlargement of accessory spleens to the size of a normal spleen after splenectomy for rupture of the spleen has been noted.

Eccles and Freer [36] reported the case of a man aged 21 who suffered a rupture of the spleen while playing football. Splenectomy was done. Ten years later the patient was reoperated on for ventral hernia, and a normal-sized accessory spleen was found in the splenic bed.

The locations of accessory spleens have been listed by Schilling [37] in the descending order of their frequency: at the splenic hilus, in the gastrosplenic omentum, in the greater omentum, along the edge of the omentum, in the splenocolic ligament, in the pleurocolic ligament and in the peritoneal tissues about the splenic venules along the pancreas. In addition, they have been reported as occurring on the intestinal wall, in the mesentery, on the greater curvature of the stomach, on the transverse colon, in the liver, in the scrotum and in the pouch of Douglas.

Finally, splenic implants may take over the function of the lost spleen. Shaw and Shafi [38] reported the case of an Egyptian man aged 20 on whom splenectomy was done some years prior to his death from cardiovascular renal disease. Autopsy revealed eighty-two splenic transplants, eighty being in the peritoneal cavity, scattered over the diaphragm, the great omentum and the pouch of Douglas, one in the left pleural cavity, on the lateral aspect of the centrum of the eighth dorsal vertebra, and the last embedded in the left margin of the liver, just beneath the capsule. Three nodules were either pedunculated or sessile, were dark red and varied from 0.2 to 2 cm.

Lee [39] described a case in which he operated for intestinal obstruction. Fifteen years previously, a splenectomy had been done for traumatic rupture of the spleen. The peritoneal cavity was studded with greenish black tumors, sessile and pedunculated, ranging from the size of a pinhead to 1 by ½ inch (2.5 by 1.2 cm.). Biopsy showed that

34. Curtis, G., and White, P.: Tr. West. S. A. **46**:364, 1937.
35. Morrison, M.; Lederer, M., and Fradkin, W.: Am. J. M. Sc. **176**:672, 1928.
36. Eccles, W., and Freer, G.: Brit. M. J. **2**:515, 1921.
37. Schilling, K.: Virchows Arch. f. path. Anat. **188**:65, 1907.
38. Shaw, A., and Shafi, A.: J. Path. & Bact. **45**:215, 1937.
39. Lee, R. T.: Lancet **1**:1312, 1923.

TABLE 15.—*Summary of Thirty Cases of Traumatic Splenic Rupture*

Case No.	Date Admitted	Date Discharged	Sex	Age, Years	History	Abdominal Examination	Associated Conditions	Results of Abdominal Tap	Laboratory Data	Pre-operative Diagnosis	Operation	Result
1	3/26/33	3/27/33	♂	43	Struck by automobile	Generalized tenderness and spasm, marked in left upper quadrant	Compound fracture left tibia, left fibula, fracture left humerus, left lower ribs; ruptured kidney and diaphragm; shock	Positive	Urine bloody R.B.C., 4,800,000 W.B.C., 8,200 Hemoglobin, 85%	Missed	None	Died
2	7/28/32	7/28/32	♂	20	Struck by automobile	Generalized tenderness and spasm, marked in left upper abdominal quadrant	Fractured left tibia, left humerus, left ribs; lacerated lung and kidney; shock	Positive	Urine bloody R.B.C., 3,800,000 W.B.C., 12,200	Made	Splenectomy	Died
3	5/ 8/32	5/16/32	♂	20	Passenger in automobile involved in accident	Upper part of abdomen rigid and tender; shifting dulness	Fractured ribs	Negative	Urine normal R.B.C., 4,000,000 Hemoglobin, 65%	Made	Splenectomy	Died
4	4/12/34	4/12/34	♂	40	Struck by automobile	Soft distention; tender right side	Crushed chest; lacerated lung and kidney; hemothorax; hemorrhage into galea	.....	Urine bloody	Made	None	Died
5	9/26/37	9/26/37	♀	27	Fall from window	Generalized tenderness and rigidity	Compound fracture of right humerus; shock; ruptured urinary bladder	.....	R.B.C., 3,500,000 Hemoglobin, 60% Urine could not be obtained	Made	Splenectomy, cystostomy	Died
6	9/15/30	11/11/30	♂	8	Struck by automobile	Tenderness appeared 24 hours after injury; spasm in left upper quadrant	Fractured ribs; dislocated clavicle	Positive	Urine normal R.B.C., 4,200,000 Hemoglobin, 70%	Made	Splenectomy	Cured
7	11/ 5/35	2/ 7/36	♀	5	Struck by automobile	Spasm in left upper quadrant	Fractured ribs and left femur; hemopneumothorax	Positive	Urine normal R.B.C., 4,100,000 Hemoglobin, 75%	Made	Splenectomy	Cured
8	10/29/33	11/ 2/33	♂	25	Fall from window	Spasm in left upper quadrant	Lacerated kidney and liver; hemothorax; subarachnoid hemorrhage	Negative	Urine bloody	Missed	None	Died
9	12/23/33	1/21/34	♂	12	Struck by automobile	Tenderness appeared 24 hours after injury; spasm in left upper quadrant	Fractured skull, left tibia, left fibula	Positive	.....	Made	Splenectomy	Cured
10	5/25/38	7/ 8/38	♂	26	No history of trauma; nausea, vomiting, and epigastric distress	Generalized tenderness and rigidity, marked in periumbilical region	[illegible]	[illegible]	.....	Missed	Splenectomy	Cured

quadrant												
10	5/25/38	7/ 8/38	♂	26	No history of trauma; nausea, vomiting, and epigastric distress	Generalized tenderness and rigidity, marked in periumbilical region	[illegible]		.....	Missed	Splenectomy	Cured
11	11/14/37	11/14/37	♀	38	Struck by automobile	Generalized tenderness	Compound fracture left tibia, left fibula; fractured ribs, pelvis; cerebral concussion; fracture of left humerus	Positive	.....	.....	None	Died
12	3/12/33	4/21/33	♂	27	Struck by automobile	Distended; tender; bulge in left flank	Fractured ribs; ruptured kidney	Positive	Urine bloody R.B.C., 4,300,000 W.B.C., 9,000 Hemoglobin, 78%	Made	Splenectomy	Cured
13	3/26/28	3/26/28	♂	8	Struck by automobile	Generalized tenderness; shifting dulness	Ruptured liver	.....	Urine normal R.B.C., 2,700,000 W.B.C., 20,000 Hemoglobin, 50%	Made	None	Died
14	8/31/29	8/31/29	♂	5	Struck by automobile	Generalized tenderness	Fractured humerus; shock	.....	Urine normal	Made	None	Died
15	1/26/30	1/26/30	♂	61	Struck by automobile	Spasm in left upper quadrant	Fractured ribs; shock; lacerated kidney	.....	Urine bloody	Made	None	Died
16	6/ 2/38	7/23/38	♀	22	Passenger in automobile involved in accident 3 weeks prior to admission; recurrent attacks of pain in chest	Tender left upper quadrant	Fractured rib	.....	.....	Missed	Splenectomy	Cured
17	2/12/38	2/12/38	♂	8	Struck by automobile	Generalized tenderness and spasm	Hemopneumothorax; mediastinal sh.ft	.....	Urine normal R.B.C., 3,200,000 W.B.C., 7,600 Hemoglobin, 60%	Made	Splenecotmy	Died
18	7/12/30	7/29/30	♂	5	Struck by automobile	Tender mass in left upper quadrant	.....	.....	.....	Made	Splenectomy	Cured
19	7/ 8/33	7/ 9/33	♂	39	Periumbilical pain, nausea, vomiting (this case has been reported as an instance of spontaneous rupture)	Distended and tender	.....	Positive	Urine normal R.B.C., 4,300,000 W.B.C., 13,800 Hemoglobin, 70%	Missed	Splenectomy	Died
20	3/12/37	3/31/37	♀	36	Passenger in automobile involved in accident 2 weeks prior to admission; sudden onset of pain in left side of chest and left shoulder	Tenderness and rigidity of upper part	.....	Positive	Urine normal R.B.C., 2,900,000 W.B.C., 6,100 Hemoglobin, 65%	Missed	Splenectomy	Cured

TABLE 15.—*Summary of Thirty Cases of Traumatic Splenic Rupture—Continued*

Case No.	Date Admitted	Date Discharged	Sex	Age, Years	History	Abdominal Examination	Associated Conditions	Results of Abdominal Tap	Laboratory Data	Pre-operative Diagnosis	Operation	Result
21	2/ 2/33	3/11/33	♂	10	Fell to curbstone	Tenderness and spasm in lower part of abdomen; shifting dulness	.....	.....	Urine normal R.B.C., 3,900,000 W.B.C., 23,000 Hemoglobin, 65%	Made	Splenectomy	Cured
22	7/30/32	8/27/32	♂	23	Fall from window	Tenderness and spasm over right side	.....	Positive	Urine normal R.B.C., 4,480,000 W.B.C., 11,200	Made	Splenectomy	Cured
23	3/31/33	5/ 9/33	♂	47	Epigastric pain, nausea and vomiting	Generalized tenderness and spasm	.....	.....	Urine normal	Missed	Splenectomy	Cured
24	12/ 7/35	12/ 9/35	♂	6	Struck by automobile	Tenderness in both upper abdominal quadrants	.....	Negative	Urine normal R.B.C., 4,000,000 W.B.C., 23,600 Hemoglobin, 80%	Made	Exploratory laparotomy	Died
25	7/14/31	8/../31	♂	32	Assault and battery	Tenderness and spasm in upper abdominal quadrants	.....	Positive	Urine normal R.B.C., 4,800,000 W.B.C., 7,800 Hemoglobin, 82%	Made	Splenectomy	Cured
26	9/16/30	10/ 1/30	♂	11	Struck by bicycle	Tenderness and spasm in upper abdominal quadrants	.....	.....	Urine normal R.B.C., 4,900,000 W.B.C., 10,000 Hemoglobin, 75%	Made	Splenectomy	Cured
27	8/16/36	9/ 1/36	♂	38	Assault and battery	Tenderness and spasm in left upper abdominal quadrant	.....	.....	Urine normal R.B.C., 4,580,000 W.B.C., 6,900 Hemoglobin, 65%	Made	Splenectomy	Cured
28	1/21/38	2/ 3/38	♀	17	Coasting accident	Tenderness and spasm in left upper abdominal quadrant	.....	.....	Urine normal R.B.C., 3,400,000 W.B.C., 7,800 Hemoglobin, 80%	Made	Splenectomy	Cured
29	9/21/35	10/ 5/35	♀	8	Struck by automobile	Abdomen distended; spasm in left upper abdominal quadrant	.....	Positive	Urine normal R.B.C., 4,800,000 W.B.C., 8,000 Hemoglobin, 70%	Made	Splenectomy	Cured
30	6/21/28	7/18/28	♂	28	Passenger in automobile involved in an accident	Tenderness and spasm in both lower quadrants	.....	.....	Urine normal R.B.C., 2,400,000 W.B.C., 9,300 Hemoglobin, 50%	Made	Splenectomy	Cured

they were normal splenic tissue. Others have reported similar cases.[40] In 1 case in which we had the opportunity to reoperate there were no splenic implants.

These implants are believed to originate from autoplastic transplants from the spleen. To support this view, attention is called to the fact that they appear only in cases in which the spleen has been removed for rupture. Removal of a diseased spleen is rarely, if ever, followed by transplants. Faltin [40b] and von Stubenrauch [40d] concluded that they develop from spleen-forming rests.

There has been much discussion as to the return of the blood picture to normal after splenectomy for traumatic rupture. Hitzrot [41] noted anemia, which persisted for a varying period but gradually returned to normal after one to three months. He also noted a change in resistance of the blood cells.

Pfeiffer and Smyth [42] have observed cases in which there was definite and persistent anemia. Connors [1] had the opportunity to observe a splenectomized patient in whom anemia persisted for seventeen years. Others have stated that anemia disappears about two months after operation.[43]

The effects of splenectomy on the blood platelets were studied by Rosenthal [44] and others,[45] who noted that there is a gradual and constant increase in the number of blood platelets, reaching its zenith during the second week. Platelet counts of 1,000,000 to 1,900,000 were observed. The platelet count begins to drop and becomes normal, or remains somewhat above normal, about the third or fourth week after operation. Observation in these cases for five years after operation has shown the platelet count to be normal or slightly above normal.

Other mentioned results of splenectomy for traumatic rupture of the spleen are hyperplasia of the peripheral lymph glands, hyperplasia of the marrow of the long bones, increase in weight, increase in appetite and decreased resistance to infection. Severe or late effects on the health and well-being of the splenectomized person are negligible or absent.

A résumé of our cases is presented in table 15.

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40. (*a*) Kupperman, W.: Zentralbl. f. Chir. **63**:3061, 1936. (*b*) Faltin, R.: Deutsche Ztschr. f. Chir. **110**:160, 1911. (*c*) Kuttner: Verhandl. d. deutsch. Gesellsch. f. Chir. **36**:25, 1907. (*d*) von Stubenrauch: ibid. **42**:213, 1912. (*e*) Smyth, C. M., Jr.: S. Clin. North America **9**:1181, 1929.

41. Hitzrot, J. M.: Ann. Surg. **67**:540, 1918.

42. Pfeiffer, D. B., and Smyth, C. M., Jr.: Ann. Surg. **80**:562, 1924. Smyth.[40e]

43. Boyd, W.: Surgical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 591. Angle and Kassel.[4]

44. Rosenthal, N., cited by Connors.[1]

45. Shore, B. R., and Kreidel, K. U.: Ann. Surg. **99**:307, 1934.

SUMMARY AND CONCLUSIONS

Subcutaneous rupture of the normal spleen is more common than is generally believed. In this hospital the condition occurred in 47.6 per cent of cases in which there was subcutaneous injury to the abdominal cavity.

There is no such clinical entity as spontaneous rupture of the normal spleen. The term should be discarded. Except for torsion with rupture, the condition in all cases is due to trauma.

A classification based on the rate of hemorrhage is submitted.

The abdominal tap is invaluable as a diagnostic procedure and should be repeated when necessary.

The differential diagnosis must exclude lesions above the diaphragm and retroperitoneal as well as intra-abdominal conditions. The diagnosis is most frequently missed because a history of trauma is not obtained or, if one is obtained, it is disregarded. Associated lesions may mask the signs and symptoms associated with a ruptured spleen.

The treatment of rupture of the spleen is surgical, and splenectomy is the operation of choice. Preoperative enemas are forbidden.

The mortality for subcutaneous rupture of the normal spleen is discussed. This mortality can be lowered by (*a*) constant alertness on the part of the surgeon and the staff to avoid errors in diagnosis; (*b*) more rapid diagnosis so that the patient will receive the benefits of operation sooner; (*c*) use of a slow blood drip preoperatively with or without intravenous administration of fluids (when blood from a "bank" is not readily available, infusions of a saline solution should be given), and (*d*) administration of adequate fluids should be given to restore water balance.

CORRELATION OF PATHOLOGIC AND CLINICAL OBSERVATIONS IN CHRONIC LYMPHOID APPENDICITIS

C. BASIL FAUSSET, M.D.
NEW YORK

A correlation seems to exist between the pathologic diagnosis of a specific type of chronic appendicitis, namely, the chronic lymphoid, and a definite symptom complex, which is herein described. The pathologic changes consist of hyperplasia of the lymphoid elements and a variable degree of fibrosis and obliteration. The clinical picture is characterized by attacks of mild to moderately severe abdominal pain, with a high incidence of nausea and occasional associated episodes of vomiting, recurring over a period lasting from months to years and never being severe enough to fall into the category of acute appendicitis.

Many appendectomies have been performed on the basis of this symptom complex, after careful exclusion, by physical examination and laboratory aid, of other pathologic lesions. In my experience such operations have often revealed relatively innocuous-appearing appendixes. This paper attempts to correlate the gross and microscopic changes in such organs with clinical findings.

Beluffi[1] in 1936 described this pathologic-clinical correlation and thoroughly dealt with the historical and bibliographic aspects of the entity up to that date. His report is based almost entirely on the histologic changes in the appendixes of 100 patients whose illness was diagnosed clinically as chronic appendicitis. He divides these changes into three fundamental types: the hypertrophic-hyperplastic, the sclerotic-atrophic and the obliterative. He considers these three types as "evolutionary stages of the same anatomical-pathological process, of which the initial lesion would be the lymphatic hypertrophy and hyperplasia; the second, an increase of the interstitial connective tissue arriving at sclerosis; the last, the complete closing of the organ." It seemed desirable to emphasize the clinical importance of the syndrome, in addition to corroborating most of Beluffi's pathologic description.

The present pathologic-clinical study is based on all the cases listed as instances of chronic lymphoid appendicitis in the files of the depart-

From the Department of Surgical Pathology of the New York Hospital and Cornell Medical College.

1. Beluffi, E. L.: Contributo all'anatomica patologica dell'appendicite cronica, Arch. ital. di anat. e istol. pat. **7**:226, 1936.

ment of surgical pathology of the New York Hospital from September 1932 to November 1938. There were 132 uncomplicated cases, in which at operation no other obvious abdominal lesion was presented. In these simple appendectomy was done. There were 50 additional cases in which the appendix was removed incidentally at the time of some other intra-abdominal operation.

MACROSCOPIC PATHOLOGIC OBSERVATIONS

The macroscopic appearance of appendixes removed from patients with chronic lymphoid appendicitis is quite variable. They measure from 4 to 12 cm. in length and from 0.6 to 1 cm. in diameter. They may be terete, fusiform, cylindric or clavate at the distal end. When the tip is clubbed, a bandlike constriction is frequently found just proximal to this. These organs are usually plump and well rounded, and palpation reveals a moderate degree of tenseness. Hyperemia is never an important feature, although a few of the serosal vessels may be minimally injected. The color ranges from light yellowish brown to dark red and moderately deep purple. The serosal surface is generally glistening and smooth, although occasionally there may be evidences of filmy adhesions on the antimesenteric surface, especially near the middle of the appendage. When such adhesions or Jackson's membrane are encountered, there is a tendency for the organ to be slightly bent on itself, forming either a J or an S, while the rarest form is that of an O, with the tip and the base in close proximity. The last is caused by a thickened, short mesentery.

As one transversely sections the organ near the tip, the mucosa in the hypertrophic and in the sclerotic type prolapses markedly, whereas in the obliterative type the central fibrous tissue extrudes. Semiformed soft feces are often expressed when the lumen is patent. Oxyurids were found in 2 specimens in this series, accompanied in 1 instance by a thin sliver of glass, measuring 8 mm. in length.

When the appendix is opened longitudinally, a small amount of pasty feces may be present, but fecaliths are rarely found. The mucosa is usually light brown or pink and is often roughly corrugated. There may be occasional petechial hemorrhages in the middle or distal third. Erosions, ulcerations or gross blood are rarely present. The lumen near the point of amputation is small in caliber, but approximately a centimeter distally it is often dilated, usually to the tip, unless there is a clubbed end. In that case a concomitant constriction of the internal surface is noted at the proximal end of the swollen tip. Other appendixes show almost no lumen and are fibrosed to the point of complete obliteration in the distal quarter.

MICROSCOPIC PATHOLOGIC OBSERVATIONS

The present microscopic description closely follows Beluffi's classification. Since the evolutionary stages of chronic lymphoid appendicitis were described by Beluffi, the attention of this department has been focused on this entity, and all of our sections have been reclassified according to the three types previously mentioned.

Hypertrophic-Hyperplastic Type.—Microscopic examination of a longitudinal section through an appendix with changes characteristic of the hypertrophic-hyperplastic type of chronic lymphoid appendicitis shows the mucosa to be largely intact. The glandular structures may be atrophic or completely absent. If present, they may appear to be rounded, stratified, and from two to four layers in thickness. The presence of any stratification, however, should be considered an artefact, because in such cases the section is not strictly radial. Throughout the length of the organ there is a wide continuous band of lymphoid tissue, composed of many discrete hypertrophied follicles, with edematous centers and conspicuous marginal sinuses, surrounded by a stroma densely packed with lymphocytes. The muscularis mucosa is indistinct. The lymphoid tissue may invade the submucosa to a moderate degree. The muscularis is normal. Considerable numbers of eosinophils are found scattered throughout the various layers in many cases. These are interpreted as confirmatory evidence of chronicity. Swollen capillaries are noted in each layer, and almost all of them are engorged with red blood cells (fig. 1).

Microscopic examination of a cross section near the tip, in an organ typical of the hyperplastic type, shows the mucosa to be intact. The glands are sparse and may or may not contain mucus-secreting cells. Most of them are small, atrophic and compressed by the neighboring overgrowth of follicles and lymphoid tissue. This lymphatic overgrowth occupies from one half to two thirds of the total surface of the appendix.

Sclerotic-Atrophic Type.—In this type of appendicitis the mucosa is also intact. Immediately subjacent to this there are one or two layers of small glands which are flattened in a longitudinal direction. Goblet cells are rare. Lymphoid follicles can still be distinguished, although they are seen to be fused with the surrounding lymphoid tissue. They have compact cellular centers and the marginal sinuses are absent. The continuous wide band of lymphoid tissue, typical of the hyperplastic variety, is, in this type, broken up and compressed by the projection into it of dense connective tissue from the submucosa. Thick sclerotic vessels traverse the submucosa. Scar tissue radiates peripherally from it to intersect the muscularis. This sclerosis is evidence of previous inflammatory insults (fig. 2).

Obliterative Type.—Obliterative appendicitis presents its most characteristic picture on transection. The lumen near the tip is entirely replaced by a continuation centralward of the fibrous connective tissue of the submucosa, which also extends peripherally to interrupt the continuity of the muscularis. A few fibroblasts and lymphocytes are noted in the sclerotic central core. Examination of a longitudinal section may reveal that the lumen is patent from the base of the organ to the distal quarter. Along the patent portion the microscopic observations

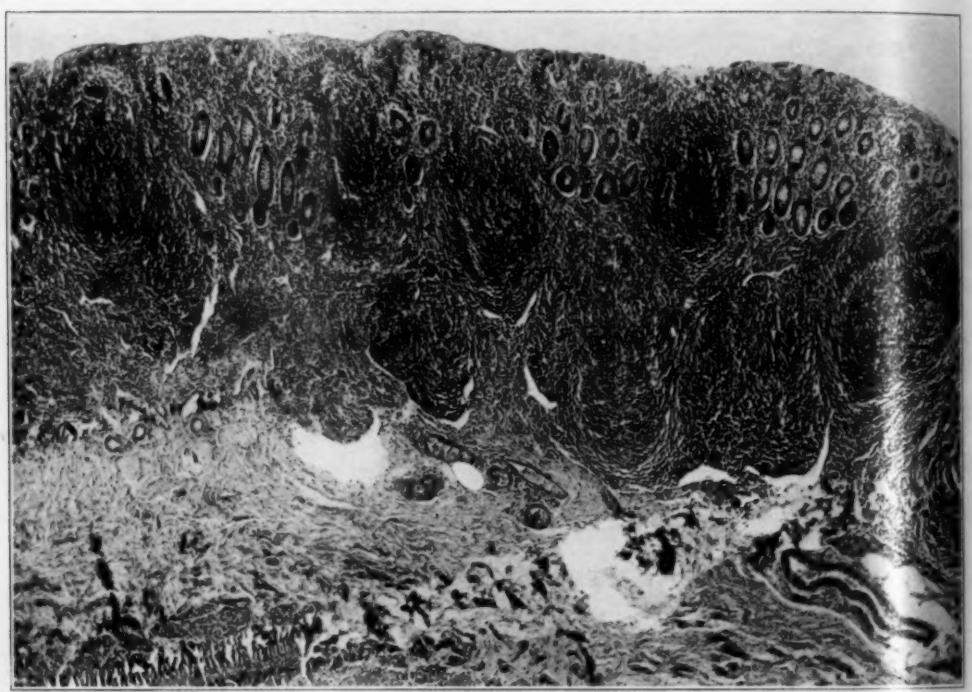

Fig. 1.—Appendix showing hypertrophic-hyperplastic appendicitis; × 39. The mucosa is intact. There is slight stratification of the atrophic glands. Discrete lymphoid follicles and a wide band of lymphoid tissue are present. The tissue used for study was fixed in solution of formaldehyde U. S. P.–alcohol, impregnated with paraffin and stained with a modified Masson (Goldner) technic.[2]

resemble those of the previously described sclerotic-atrophic type, except that there is a complete absence of lymphoid tissue.

Polymorphonuclear leukocytes, as a rule, are absent in each of these three types, although occasional appendixes may show a superimposed moderately acute flare-up. The nerve plexuses of Auerbach and Meissner are not remarkable in this series. The same is true of the

2. Goldner, J.: A Modification of the Masson Trichrome Technique for Routine Laboratory Purposes, Am. J. Path. **14**:237, 1938.

subserosa and serosa except that the latter in a few instances shows the presence of filmy adhesions. In rare cases the lymphatic spaces contain numerous leukocytes, including polymorphonuclears, but these are not widely distributed throughout the tissue.

By way of comparison, the chronic ulcerative type of appendicitis will be described. In this the mucosa is irregular and contains numerous minimal erosions and ulcerations along its surface (fig. 3). Each of these is surrounded by a zone of lymphocytes and polymorphonuclear leukocytes. Lymphoid tissue is present in diminished amount, or it

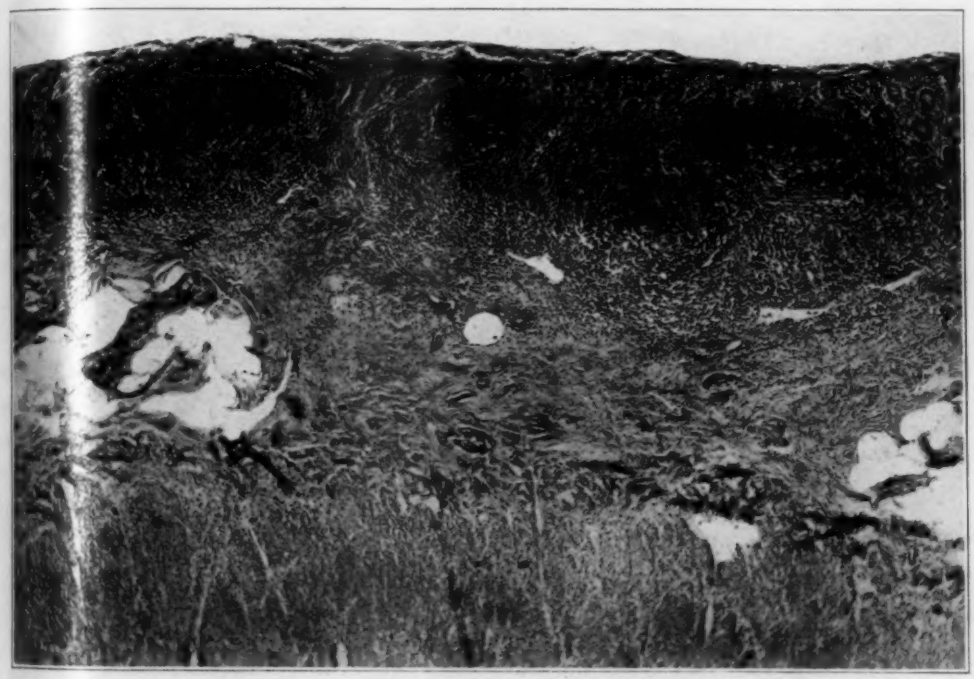

Fig. 2.—Appendix showing sclerotic-atrophic appendicitis; × 39. The glands are flattened beneath the intact mucosa. The lymphoid follicles are fused. The lymphoid tissue is diminished in amount as compared with a similar field in figure 1.

may be entirely wanting. The blood vessels are increased in number and are dilated. Many leukocytes, particularly polymorphonuclear leukocytes, are noted in the mucosa, submucosa and muscularis. There is a definite increase in the fibrous connective tissue of the submucosa, which also is likely to be heavily infiltrated with fat cells. The muscularis is hypertrophied and crossed by fibrous connective tissue strands. Auerbach's plexuses are hyperplastic and may contain atypical ganglion cells. The serosa is usually very greatly thickened. In short, chronic ulcerative appendicitis shows pathologic changes in every layer, whereas in

chronic lymphoid appendicitis abnormalities are confined largely to the mucosa and submucosa. Both this and the sclerotic-atrophic type lead ultimately to fibrous obliteration of the lumen.

CLINICAL OBSERVATIONS

Of the 132 patients with uncomplicated chronic lymphoid appendicitis, 48 were males and 84 females. Nausea was present in 60 per cent; nausea and vomiting combined, in 30 per cent; 2 patients induced

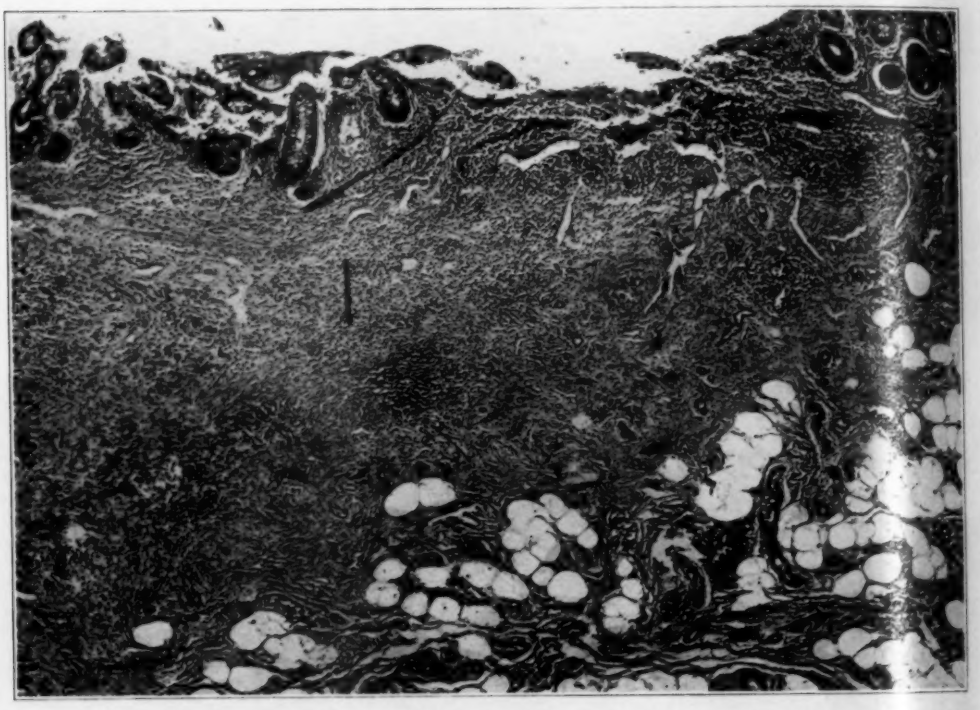

Fig. 3.—Appendix showing chronic ulcerative appendicitis; × 44. The mucosa is ulcerated, and there is a surrounding zone of lymphocytes and polymorphonuclear leukocytes. No lymphoid tissue is present. The submucosa contains considerable scar tissue and is infiltrated with fat. Polymorphonuclear leukocytes are seen in each layer.

vomiting, and 1 patient vomited during spasms of coughing. Forty per cent had neither nausea nor vomiting. The percental distribution of appendectomies according to decades of life was as follows: 1 to 10, 11 per cent; 11 to 20, 39 per cent; 21 to 30, 25 per cent; 31 to 40, 20 per cent; 41 to 50, 3.5 per cent; 51 to 60, 1.5 per cent.

Since there is a physiologic hyperplasia of the lymphoid elements in children and adolescents, the appendixes removed in the first two decades may be interpreted as not abnormal except that in these organs occurred

the largest percentage with mild infiltration by polymorphonuclear leukocytes. One patient in this group had an appendical abscess drained one year before appendectomy, but on microscopic examination, interestingly enough, there was no pathologic change except lymphoid hyperplasia.

One of the striking features of this study is that 66 of the 132 patients gave a history of recurring attacks of pain in the right lower quadrant of the abdomen over a period of from one to ten years. Many of these patients used the words "several years" in describing the duration of symptoms attributable to chronic appendicitis. Of the remaining 66 patients, 24 complained of similar symptoms for from one to several months, whereas 42 noted abdominal distress over a period of from a

TABLE 1.—*Location of Abdominal Pain*

Location	Cases	
	Number	Per Cent
Right lower abdominal	77	58
Generalized abdominal	25	38
Epigastric	16	
Umbilical	7	
Right and left lower abdominal	5	4
None	4	

TABLE 2.—*Examining Surgeon's Interpretation of Abdominal Tenderness and Muscle Spasm*

	Tenderness					
	Slight	Moderate	Acute	Rebound	None	Muscle Spasm
Cases	40	46	4	10	20	12
Percentage	30	35	3	8	15	9

few hours to three weeks. The percentage in whom abdominal pain originated and remained in the right lower quadrant and at McBurney's point was 58; patients with vague abdominal, epigastric and umbilical distress localizing in the right lower quadrant constituted another 38 per cent; the other 4 per cent had either mild discomfort in both lower quadrants of the abdomen or no localized pain (table 1).

On palpation of the abdomen 71 per cent of the patients complained of discomfort in the right lower quadrant or at McBurney's point; 14 per cent had tenderness at the umbilicus or in both lower abdominal quadrants, and 15 per cent had none at any location.

Since a major operation was contemplated, it is significant to note that tenderness, interpreted by the surgeon, was acute in but 3 per cent, moderate in 34 per cent, and slight in 50 per cent. In addition to discomfort, 9 per cent had spasm of the right rectus or obliquus muscles and 8 per cent had rebound tenderness referred to McBurney's point. The remainder, or 15 per cent, had no distress, as indicated in table 2.

The preoperative temperatures of these patients averaged 37 C. (98.6 F.), with some slightly subnormal and others a few tenths of a degree above normal. Further evidence of the chronic nature of this disease is found in the study of the white blood cell counts. In 55 per cent of the cases the leukocytes numbered from 5,000 to 10,000, in 42 per cent from 10,000 to 15,000 and in 3 per cent more than 15,000 per cubic millimeter.

No study has been made regarding the follow-up on the patients, since many were on the Private Pavilion and there are no available data. Data on those who have been operated on within the last year

TABLE 3.—*Cases in Which Incidental Appendectomies Were Performed*

Operation	Cases		
	Number	Per Cent	
Gastroenterostomy	3	6	Hysterectomy
Cholecystectomy	20	40	Uterine ventral suspension
Operation on female generative organs	20	40	Oophorectomy
			Salpingectomy
Resection of ascending colon for carcinoma of cecum	1	2	Operation for bleeding graafian follicle
Operation for mesenteric adenitis	3	6	Dilatation and curettage
Removal of Meckel's diverticulum	1	2	
Operation for terminal ileitis	1	2	
Higgin's bilateral ureteral transplant	1	2	

TABLE 4.—*Data on Five Complicated Cases in Which Variations from the Average White Cell Count and the Average Temperature in Uncomplicated Cases Were Found*

Temperature	Lesion	Leukocytes per M
38.4 C. (101.1 F.)	Mesenteric adenitis	20,400
38.4 C. (101.1 F.)	Salpingitis	16,000
37.6 C. (99.6 F.)	Salpingitis	26,000
38.2 C. (100.7 F.)	Bleeding graafian follicle	10,200
37.0 C. (98.6 F.)	Cholecystitis	21,650

also cannot be of value from this standpoint. There were few complications. One patient had a wound infection requiring drainage. Two patients had unexplained fever of 39 C. (102.2 F.) or more, and another had leukocytosis (white cell count above 15,000) during the entire week after operation. All these recovered. There were no deaths.

Those cases in which an incidental appendectomy was done during the course of another intra-abdominal operation total 50 and are classified as cases of asymptomatic pathologic conditions of the appendix. These are listed in table 3.

One is reluctant to exclude a number of these cases, in which gastrointestinal symptoms were a feature for many years, from the group of the symptom complex of chronic appendicitis, since many of the female patients were found to have pathologic changes in the generative organs

at operation, such as bleeding graafian follicles, ovarian cysts and retroverted uteri. An analysis of the findings in this group closely parallels those in the uncomplicated group. There were 12 males and 38 females. Nausea occurred in 44 per cent, vomiting in 26 per cent, and neither in 56 per cent. The white cell counts and temperatures varied from the average in the preceding series in 5 instances (table 4).

Operation was performed between the ages of 20 and 50 in 78 per cent of the patients. Sixty-eight per cent had complained of abdominal pain over a period of from one to many years, and 14 per cent had noted symptoms for several months. Distress occurred in the right upper quadrant of the abdomen in 30 per cent and in the right lower quadrant in 28 per cent, and umbilical, epigastric or generalized abdominal pain in 28 per cent. A group without abdominal pain included those with menorrhagia, metrorrhagia or sterility. Therefore, it seems from the foregoing figures that the symptoms of at least half of these patients could be explained more clearly on the basis of chronic appendicitis than on that of the other operative finding. The latter may, in reality, be the incidental finding and chronic appendicitis the primary lesion. It is granted that in such cases biliary tract disease, peptic ulcer, terminal ileitis or Meckel's diverticulum could easily share symptoms with chronic appendicitis.

Chronic lymphoid appendicitis is an apparently definite pathologic and clinical entity which accounts for many cases of "chronic appendicitis" in which the surgeon is disappointed at the comparatively normal-looking organ he has removed, one which is in reality abnormal, as shown in this study.

SUMMARY

The pathologic changes in a specific type of appendicitis, namely, chronic lymphoid appendicitis, have been described.

One hundred and thirty-two cases of chronic lymphoid appendicitis have been analyzed clinically. Symptoms were present for as long as ten years; vomiting occurred in 50 per cent; pain usually focused in the right lower quadrant of the abdomen; spasm of the abdominal muscles and rebound tenderness were rare; the temperature was normal and the leukocyte count ranged between 5,000 and 15,000.

The pathologic diagnosis of chronic lymphoid appendicitis has been found to coincide with the clinical syndrome described.

Fifty incidental appendectomies have been tabulated, and the importance of the appendical lesions has been stressed.

CAPILLARY PERMEABILITY AND INFLAMMATION IN NARCOTIZED RABBITS

RALPH D. CRESSMAN, M.D.
AND
R. H. RIGDON, M.D.
NASHVILLE, TENN.

A difference in the response of narcotized and of normal animals has been observed in anaphylactic shock. Besredka [1] found that sensitized guinea pigs which received the shocking reinjection while under ether anesthesia showed no anaphylactic symptoms. Banzhaf and Famulener [2] obtained similar results with chloral hydrate. Farmer [3] recently has shown that ethyl carbamate (urethane) administered to sensitized guinea pigs prior to the shocking reinjection led to the survival of 15 of 30 animals. Besredka explained the action of the narcotic by assuming that the ether "allowed the nerve cell to remain indifferent to the union" of the antigen and antibody. Farmer, however, stated the opinion that this effect of a narcotic is probably attributable to its peripheral action on the bronchial musculature. The exact mechanism by which anesthesia may alter the animal's reaction is apparently not clearly understood.

Dale and Laidlaw [4] have pointed out that rabbits under ethyl carbamate (urethane) anesthesia fail to show the depressor vasodilator response to small intravenous injections of histamine. Abel and Geiling [5] observed that capillary dilatation in the skin and mucous membranes was either absent or markedly diminished when dogs were anesthetized with ether before receiving an intravenous injection of albumoses. Krogh [6] has shown that local anesthesia either partly

From the Departments of Surgery and Pathology, Vanderbilt University.

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1. Besredka, A.: Comment pent-on combattie l'anaphylaxie? Ann. Inst. Pasteur **21**:950, 1907.

2. Banzhaf, E., and Famulener, L.: The Influence of Choral Hydrate in Serum Anaphylaxis, J. Infect. Dis. **7**:577, 1910.

3. Farmer, L.: The Influence of Narcotics on Anaphylactic Shock, J. Immunol. **32**:195, 1937.

4. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of B-iminazolylethylamine, J. Physiol. **41**:318, 1910.

5. Abel, J. J., and Geiling, E. M. K.: Some Hitherto Undescribed Properties of the Constituents of Witte's Peptone, J. Pharmacol. & Exper. Therap. **23**:1, 1924.

6. Krogh, A.: The Anatomy and Physiology of the Capillaries, ed. 2, New Haven, Conn., Yale University Press, 1929, p. 170.

or completely inhibits the development of macroscopic evidence of inflammation. Hirschfelder [7] and Langley [8] failed to confirm this observation. Pickrell [9] recently has stated that alcoholic intoxication maintained at the point of stupor destroys the resistance of rabbits to pneumococcic infection. This loss of resistance, according to Pickrell, "appears to be due to the fact that intoxication profoundly inhibits the vascular inflammatory response as long as the intoxication is maintained." Pickrell stated that in the absence of capillary dilatation and of margination of the leukocytes leukocytic emigration at the site of infection is negligible and the bacteria therefore proliferate uninterruptedly. Similar experiments show that "ether or avertin anesthesia has as marked an inhibitory effect on the inflammatory response as has alcoholic intoxication, and produces as marked a loss of resistance to infection." The significance of Pickrell's observations if such a process should occur in the human being is obvious.

In the present paper the capillary permeability and the inflammatory reaction have been studied in rabbits and mice, the former by observation of the localization and concentration of trypan blue in areas of rabbits' skin treated with xylol and the latter by macroscopic and microscopic observation of skin previously treated by intradermal injections of aleuronat, infusion broth cultures of staphylococci and cultures of Pneumococcus type III. The anesthetics used in this study were alcohol, ether and pentobarbital sodium.

EXPERIMENTS

Effect of Anesthesia on the Localization of Trypan Blue in Areas of Inflammation Produced by Xylene.—The localization and concentration of trypan blue in areas of inflammation produced by application of xylene to the rabbit's skin has been described by Rigdon.[10] The method is as follows: The rabbit's skin is carefully shaved twenty-four to forty-eight hours before use. Squares of skin are marked out with india ink, and xylene is painted on different areas of the same rabbit with a cotton applicator without rubbing, usually at intervals of ninety, sixty, forty-five, thirty and fifteen minutes and immediately before intravenous injection of 10 cc. of 0.2 per cent trypan blue. Each side of the animal may be used if duplicate results are desired.

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8. Langley, S. N.: Antidromic Action, J. Physiol. **58**:49, 1923.

9. Pickrell, K. L.: The Effect of Alcoholic Intoxication and Ether Anesthesia on Resistance to Pneumococcal Injection, Bull. Johns Hopkins Hosp. **63**:238, 1938.

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The effect of alcohol, ether and pentobarbital sodium anesthesia on the localization and concentration of trypan blue was studied. Rabbits weighing 2 to 3 Kg. were given 60 cc. of 20 per cent ethyl alcohol by stomach tube; this usually produced a deep stupor comparable to surgical anesthesia. Additional amounts of alcohol were given during the experiments when indicated. Ether was given by inhalation, the animal being kept under light surgical anesthesia. Pentobarbital sodium was administered intravenously in an initial dose of 30 mg. per kilogram of body weight, with the subsequent addition of smaller doses as needed to maintain anesthesia. Pentobarbital gave the lightest anesthesia of the three anesthetics used. The application of xylene was begun after anesthesia had been obtained.

In the normal rabbit, as seen in a large number of animals and as previously described by Rigdon,[10] trypan blue localizes and concentrates in a characteristic fashion in cutaneous areas of inflammation produced by xylene. Within one minute after the dye is given intravenously it can be seen staining the area to which xylene was applied immediately before, and its concentration increases rapidly. Shortly thereafter the dye begins to appear and concentrate in the areas painted with xylene fifteen and thirty minutes before. Occasionally dye first appears in the area painted fifteen minutes earlier and in one-half to one minute is seen in the area to which xylene was applied immediately before injection. Thirty minutes after the dye is given, a regular gradation of intensity of staining of the painted areas is seen. The area to which xylene was applied immediately before the injection is intensely blue, with progressively less dye in the areas painted fifteen, thirty, forty-five, sixty and ninety minutes earlier. Areas to which xylene has been applied longer than ninety minutes before the dye was given showed no greater concentration than the surrounding skin.

In anesthetized animals the order in which trypan blue localizes is altered. In 5 animals intoxicated with alcohol dye appeared first in the area treated with xylene fifteen minutes before giving the dye, and two to twenty-five minutes later it first could be determined to be present in the area treated immediately before injection of dye. Figure 1 demonstrates the difference between the normal and the alcohol-treated rabbits. The areas were treated with xylene fifteen minutes before, five minutes before and immediately before the dye was given, and the photograph was taken twenty minutes after. The control animal had the greatest amount of dye in the area treated with xylene immediately before, with progressively less in the areas treated five and fifteen minutes before. The rabbit anesthetized with alcohol had the greatest concentration of dye in the area painted fifteen minutes before, with progressively decreasing amounts in the remaining two areas. The duration of alcoholic intoxication apparently did not influence the alteration in localization and concentration of trypan blue. The reaction was the same in rabbits given the dye one hour after intoxication and in rabbits to which the injection was given after six hours of alcoholic stupor.

The rabbits anesthetized with ether (3 rabbits) showed the same type of localization of dye as the animals treated with alcohol, with slightly less delay in appearance of the dye. From three to seven minutes elapsed between the first staining in the skin treated fifteen minutes before and its appearance in the area treated immediately before injection of trypan blue.

Pentobarbital caused the least delay in the localization of dye, which appeared one to two and one-half minutes later in the area painted with xylene immediately before than in that painted fifteen minutes before. This was of interest in view of the type and depth of anesthesia.

Inflammation Produced by Xylene, Aleuronat and Bacteria in Anesthetized Animals.—Rabbits intoxicated with alcohol as described were used for the study of the inflammatory response. Application of xylene to normal rabbit skin is followed shortly by hyperemia with subsequent edema. At six to eight hours the skin is definitely edematous and slightly red (there is some variation among normal rabbits in the extent and degree of edema). Six rabbits intoxicated with alcohol all demonstrated hyperemia and edema on application of xylene to the skin, which were not noticeably different from the reactions of normal rabbits either immediately or at the end of eight hours, when the animals were killed by a blow on the head and the treated areas were removed for microscopic section.

Microscopic sections of the cutaneous areas treated with xylene in the rabbits given alcohol showed a definite decrease in the number of leukocytes present as

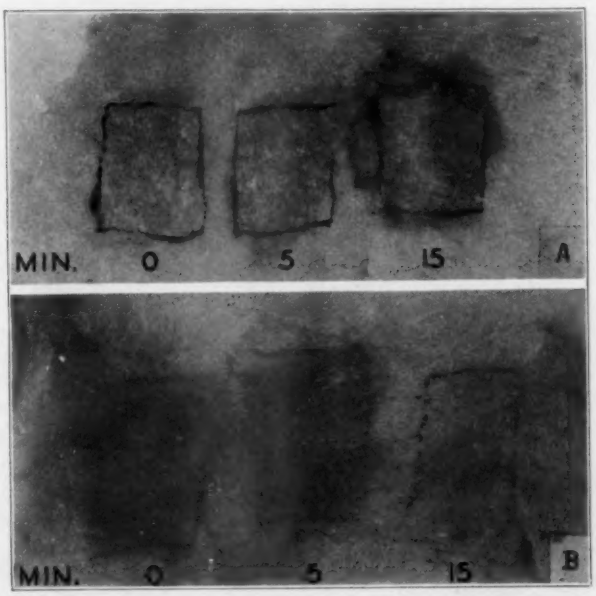

Fig. 1.—Cutaneous areas of (*A*) a rabbit intoxicated with alcohol and (*B*) a nonintoxicated rabbit, treated with xylene fifteen minutes, five minutes and immediately before intravenous injection of 10 cc. of trypan blue. The photograph was taken twenty minutes after the dye was given. In *A* the greatest amount of dye is in the area treated with xylol fifteen minutes before the injection; in *B* the greatest concentration is in the area treated with xylene immediately before the dye was given.

compared with lesions of similar age in the skin of the normal rabbit. In the xylene-treated skin of the normal rabbit the leukocytes were located primarily in the dermis, with the greatest number adjacent to the epidermis. The leukocytes were present in the lumens and about the peripheries of the small blood vessels. In the anesthetized animals there was absence of leukocytes in the lumens of the small vessels. This fact suggests that some effect was produced in the rabbit which prevented the leukocytes from concentrating in the small vessels rather than that the leukocytes were unable to pass through the vessel wall.

Figure 2 demonstrates the difference in the number of leukocytes in the xylene-treated skin after eight hours in an intoxicated and in a control rabbit.

The reaction to aleuronat was observed in a group of 4 rabbits anesthetized with alcohol and in a group of 4 control rabbits. Two-tenths cubic centimeter of a 1 per cent suspension of aleuronat in 0.9 per cent saline solution was injected intradermally into two cutaneous areas in each rabbit. In four hours there was an area of edema 1 cm. across, without hyperemia, in both groups. Some hyperemia was present, and a variation between animals in the same group was noted, but on the whole no greater reaction was seen in the control group than in the intoxicated animals at the end of eleven hours, when the animals were killed and the lesions removed for microscopic study.

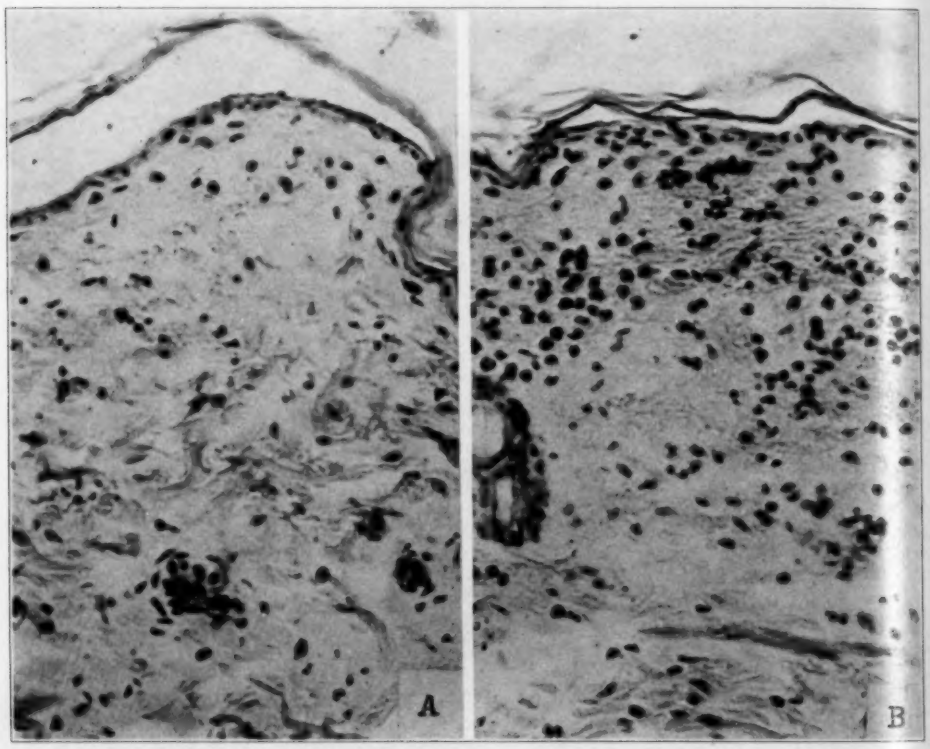

Fig. 2.—Sections through an area of skin eight hours after application of xylene. *A*, section of the skin of a rabbit intoxicated with alcohol; *B*, section of the skin of a nonintoxicated rabbit. The difference in the number of leukocytes is marked.

In sections the aleuronat appeared in the dermis as a mass of fragmented pink-staining material. Infiltrating this and the surrounding tissue were leukocytes. The number of leukocytes in the lesions of the normal animals was greater than in those of the intoxicated animals (fig. 3).

To determine whether the effect of alcohol on the reaction induced by organisms paralleled that induced by xylene and aleuronat, 6 rabbits intoxicated with alcohol were given intradermal injections of 0.5 cc. of a broth culture of a non-toxin-producing Staphylococcus aureus and 5 intoxicated rabbits were given injections of 0.2 cc. of a culture of Pneumococcus type III. Five nonintoxicated rabbits

were similarly inoculated with staphylococci and 5 with pneumococci. In each rabbit the injection was given in two areas. In each of 3 intoxicated rabbits and in 1 nonintoxicated rabbit staphylococci and pneumococci were injected on opposite sides for comparison.

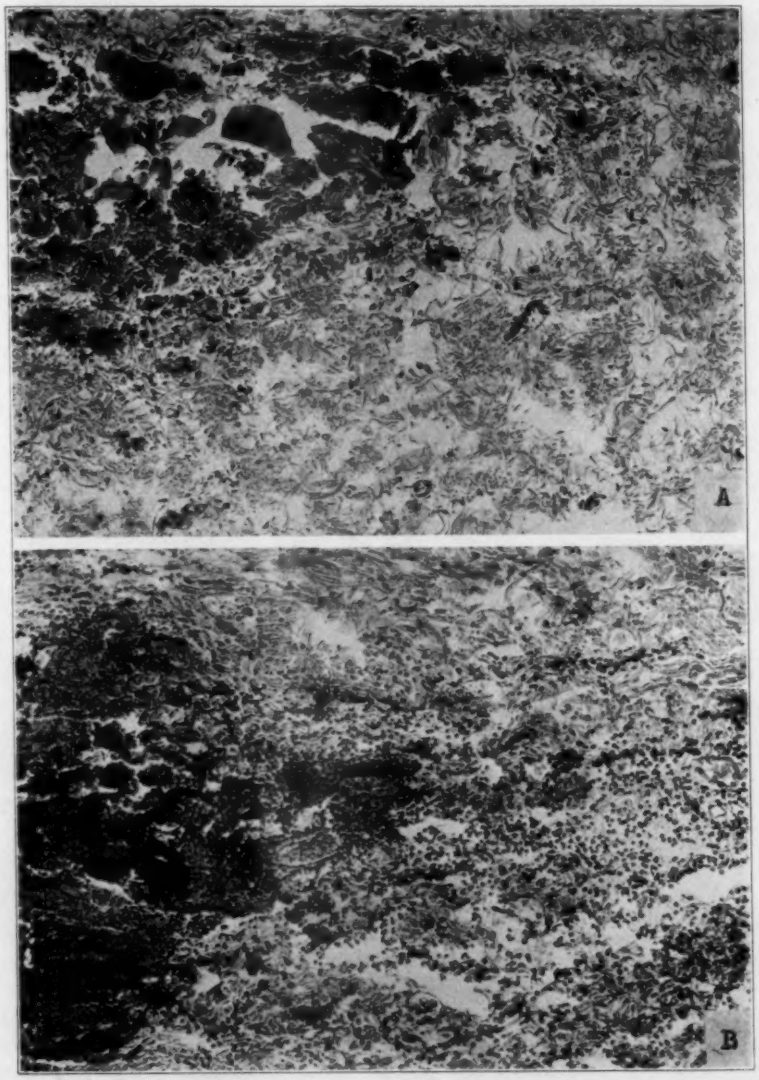

Fig. 3.—Section through the skin into which aleuronat was injected, after eleven hours. *A*, skin from a rabbit intoxicated with alcohol; *B*, skin from a nonintoxicated rabbit. The difference in the number of leukocytes about the mass of aleuronat is evident.

In the nonintoxicated animals, after six hours all the areas inoculated with organisms showed hyperemia and edema, which in some were moderate and in

others intense. A few of the intoxicated rabbits, both with staphylococci and with pneumococci, showed a very slight or a barely perceptible reaction at the site of inoculation, but some showed a moderate amount of hyperemia and edema, as great as that observed in some of the nonintoxicated group. In the same animal pneumococci and staphylococci gave parallel reactions; that is, both gave slight reactions or both gave moderate reactions. On the whole, the nonintoxicated rabbits showed more severe gross lesions than did the intoxicated rabbits. The animals were killed after six hours for microscopic study of the lesions.

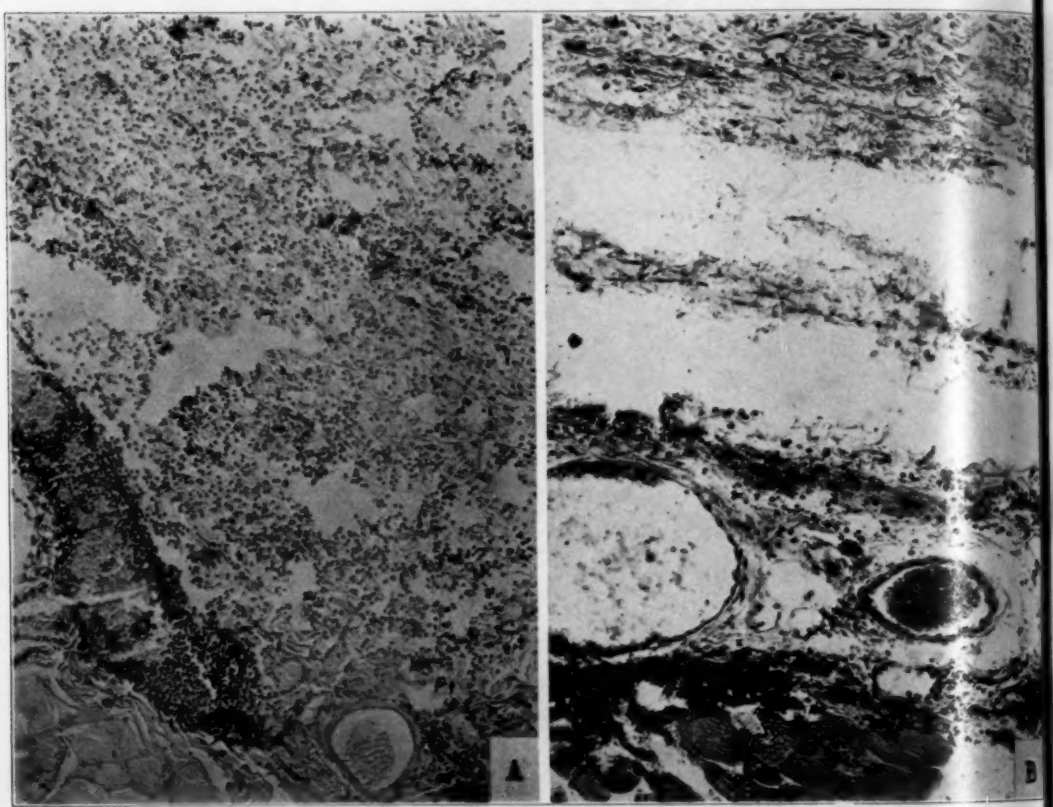

Fig. 4.—Sections through the subcutaneous tissue six hours after the injection of staphylococci. *A*, tissue from a nonintoxicated rabbit; *B*, tissue from a rabbit intoxicated with alcohol. A large number of leukocytes are present in the lumen of the vessel and diffusely infiltrate the tissue in *A*. Essentially all the bacteria are phagocytosed in the normal animal, while large masses of bacteria with essentially no leukocytosis or phagocytosis are seen in the intoxicated rabbit.

In the rabbits intoxicated with alcohol, in two of the five cutaneous lesions due to pneumococci there was a marked decrease in the number of leukocytes about the bacteria, with many of the bacteria not phagocytosed. The remaining three showed essentially the same leukocytic picture as the controls; that is, many leukocytes in the tissue, with practically all the bacteria phagocytosed.

Of the six cutaneous lesions due to staphylococci in intoxicated rabbits, 2 showed a marked decrease in the number of leukocytes, many bacteria remaining unphagocytosed (fig. 4 *A*). The remaining four lesions demonstrated the presence of many leukocytes with phagocytosis of bacteria similar to that present in the cutaneous lesions of the control rabbits (fig. 4 *B*).

In 5 rabbits anesthetized with ether and with xylene applied to the skin, the hyperemia and edema which developed were grossly the same as those observed in the controls. Microscopic section of the xylene-treated skin removed at six hours showed a decreased number of leukocytes in the area treated with xylene as compared with the skin of normal animals.

Two rabbits anesthetized with ether were given injections of aleuronat in the same way as the rabbits treated with alcohol. At the end of six hours the lesions showed the same amount of edema and hyperemia as was seen in the controls. Microscopic study of the sections of skin revealed a diminution in the number of leukocytes about the aleuronat as compared with the normal reaction.

Pentobarbital sodium similarly did not change the gross imflammatory reaction of the skin to xylene in 5 rabbits or to aleuronat in 4 rabbits. Sections of the skin of the xylene-treated areas after six hours showed practically the same number of leukocytes as the controls. This was true also of sections through the lesions produced by aleuronat. The variation in this group was apparently as great as in a group of normal rabbits.

Mice were used in one group of experiments, in which ether was the anesthetic. Twenty-one mice were used, 14 anesthetized mice and 7 controls. The animals were anesthetized in a large jar containing sufficient ether to maintain anesthesia. After they were anesthetized, 0.05 cc. of a milky saline suspension of washed staphylococci was injected subcutaneously in each flank of the anesthetized and of the control mice. At one hour intervals up to six hours, 2 anesthetized mice and 1 control mouse were killed, the amount of edema and hyperemia at the site of injection being noted and the tissues fixed for microscopic sections. The macroscopic reaction to the bacteria was the same in the anesthetized and in the control mice.

Sections through the sites of inoculation of bacteria showed that the number of leukocytes increased with the increasing interval between the time the bacteria were injected and the time the animals were killed. There was no difference in the number of leukocytes or the degree of phagocytosis in the two groups of mice.

COMMENT

The results of these experiments indicate that the inflammatory response to an irritant, either bacterial or chemical, is different in a normal rabbit and in a rabbit narcotized with alcohol or ether. Edema and hyperemia are either partly or completely inhibited in the anesthetized rabbit as compared with the normal. There is also a marked diminution in the number of leukocytes in the areas of inflammation in the skin in the narcotized rabbits. The number of animals used in the different groups in these experiments was small; however, it is obvious that a variation occurred in the narcotized rabbits. Some of the rabbits given alcohol or ether showed a reaction similar to that seen in the normal rabbits. This variation in anesthetized rabbits differs from the results obtained by Pickrell, who found that his intoxicated rabbits in

all instances showed essentially no inflammatory changes in the areas of skin inoculated with cultures of pneumococci.

The permeability of the capillaries as demonstrated by the localization and concentration of trypan blue in areas of skin treated with xylene is different in a rabbit given either alcohol or ether from that in the normal animal, as is shown by the altered order of localization and concentration of the dye. In the normal animal trypan blue localizes and concentrates first in the area to which xylene has been applied immediately before the dye is given, in contrast to its localization and concentration first in the areas to which xylene was applied fifteen minutes before injection of the dye in the rabbits given either alcohol or ether.

Although there is a definite difference in capillary permeability in the normal and the anesthetized rabbit as shown by the localization and concentration of trypan blue, we cannot completely agree with Pickrell that "in the intoxicated body the capillaries fail to respond to the presence of an inflammatory irritant with dilatation and an increase in their permeability."

Microscopic studies of skin of anesthetized rabbits into which staphylococci or pneumococci were injected showed a diminution in the number of leukocytes in the extravascular tissue and a failure of these cells to concentrate in the lumens of the blood vessels. This variation in the number of leukocytes may be responsible for the marked difference in the number of bacteria which have not been phagocytosed. This absence of phagocytosis may permit a more rapid multiplication and spread of the infection.

A series of papers has recently been published by a group of German workers [11] on the macroscopic variation in the early inflammatory reaction following the administration of certain drugs. The variation in the severity of the reactions in the different groups of rabbits was correlated with the respiratory activities of the animals treated with different drugs. The mechanism diminishing the inflammatory response was considered to be one of respiratory depression leading to a decrease in hydrogen ion concentration of the blood, an increase in the tissue and a reduction in the inflammatory response to mustard oil. Observations

11. (*a*) Lipschitz, W.: Studien zur Pharmakologie der Entzündung: I, Arch. f. exper. Path. u. Pharmakol. **151**:267, 1930. (*b*) Peng, D.: II. Die Atmungs- und Entzündungshemmung am Kaninchen durch Urethan, ibid. **151**:270, 1930. (*c*) Guggenheim, K.: III. Pharmakologische Beeinflussung von Entzündungsvorgängen durch Einwirkung auf die Lungenventilation: Schlafmittel Cardianol, ibid. **151**:279, 1930. (*d*) Winkler, H.: IV. Die Atmungs- und Entzündungshemmung durch Bromid und die Entzündungsnachwirkung des Urethans, ibid. **151**:302, 1930. (*e*) Fröhlich, H.: V. Die Veränderung der Blutreaktion und des Kohlensäurebindungsvermögens des Plasmas von Kaninchen unter dem Einfluss atmungs- und entzündungshemmender Pharmaka, ibid. **151**:323, 1930.

on the frequency and depth of respiration in the rabbits used in our experiments failed to reveal a variation which was considered significant. The number of leukocytes in the circulating blood did not parallel increases or decreases in the inflammatory response in the control or in the narcotized rabbits.

It would appear from our studies that a rabbit anesthetized with pentobarbital responds to the application of xylene, aleuronat and bacteria more like the normal animal than does a rabbit given alcohol or ether. This is interesting in view of some of the other differences in action between the barbiturates and ether, among them the observation of Bollman and his associates [12] that a difference in concentration of the blood occurred in dogs anesthetized with ether as compared with those anesthetized with amytal. Knoefel [13] also has pointed out that the overstimulation of the sympathetic nervous system and the increased output of epinephrine occurring with ether may be prevented by barbiturates. The failure to observe any difference in the number of polymorphonuclear leukocytes in the cutaneous areas of control or etherized mice in which staphylococci were injected subcutaneously suggests that the effects produced by anesthesia on the inflammatory response may vary in different species.

CONCLUSIONS

1. Capillary permeability in areas of inflammation is altered in rabbits narcotized with alcohol or ether, as demonstrated by the localization and concentration of trypan blue.

2. The inflammatory response may be greatly or only slightly diminished in rabbits narcotized with alcohol or ether, as indicated by the amount of hyperemia, edema and leukocytosis in response to chemical and bacterial irritants.

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12. Bollman, J. L.; Svirbely, J. L., and Mann, F. C.: Blood Concentration Influenced by Ether and Amytal Anesthesia, Surgery **4**:881, 1938.

13. Knoefel, P. K.: Anesthesia and the Sympathetic Nervous System, Anesth. & Analg. **15**:137, 1936.

JOINT CARTILAGE UNDER INFRAPHYSIOLOGIC, ULTRAPHYSIOLOGIC AND EUPHYSIOLOGIC DEMANDS

ERNST FREUND, M.D.
LOS ANGELES

The importance to osseous structures of functional efficiency is common knowledge. The Hueter-Volkmann pressure theory, Wolff's law of transformation of bone and Roux's principle of the functional stimuli of pressure and tension have been widely recognized, and the idea that osseous tissue apart from the important factor of heredity is in need of function for its development and preservation has been accepted even by the laity. Physicians are accustomed to observe that osseous tissue adapts itself to changes of functional conditions; it increases under augmented function and decreases in regions in which function is diminished, and this process of adaptation is associated with a complete change of its inner architecture—extensive replacement of the old osseous tissue by new tissue more fit for the new purpose. The process of resorption and apposition of bone which is continuously at work to fulfil the daily demands of altered statics is one of the cardinal features in the biologic nature of the skeleton.

Far less common is the knowledge that the cartilaginous tissue also lives and under normal conditions responds to certain functional stimuli which are as important for growth and existence of cartilage as pressure and tension are for bone. The relatively small amount of cartilaginous tissue present in the adult organism has apparently kept down interest in essentially the same questions which for osseous tissue found conclusive answers several decades ago. It is surprising that cartilaginous tissue, which plays such an important role in the phylogenetic and ontogenetic development and the catabolic changes of which are of such great influence in adult life, has evoked but little interest from a biologic standpoint. For the existence of cartilaginous tissue genetic factors are of intrinsic importance, and many structural changes not to be explained simply on a mechanical or a dynamic basis find adequate explanation in a consideration of embryonal processes or evolution. Cartilage is a supporting substance which, after it has served its developmental task as predecessor of bone tissue, is present in relatively few regions, where

From the Department of Orthopedic Surgery, College of Medical Evangelists.

it needs for its further existence and development certain functional stimuli that may be considered almost specific.

I am mainly concerned in this article with some of the biologic properties of joint cartilage. The behavior of cartilage under ultraphysiologic conditions (increased pressure) and infraphysiologic conditions (disuse) will be discussed especially. From such an analysis it will appear that joint cartilage reveals its normal, highly differentiated (functional) structure as long as the biologic stimuli exercised on it range within physiologic limits. There will be alteration of structure yielding quickly to lasting damage as soon as the duration of the stimuli exceeds the normal. Joint cartilage, like every other highly differentiated tissue, has been rendered almost unable to compensate for pronounced catabolic changes by its lack of power of regeneration, which is only a result of the extreme degree of adaptation of this tissue to function. In order to understand this characteristic of joint cartilage it is necessary to be well informed about the normal structure of cartilaginous tissue.

Dependent largely on function, the architecture of articular cartilage varies considerably from joint to joint. There is a different picture in a weight-bearing joint of the lower extremity, where a great deal of pressure is exercised on the joint ends, from that in a smaller joint of the arm (a finger joint, for instance), where pressure is relatively mild. The smaller joints, less complicated in their function, show less differentiation in their cartilaginous structure. Age is another important factor. In infancy and youth the structure of joint cartilage, even in the larger articulations of the lower extremities, is less mature. It reaches its full development as a mechanical-functional structure when skeletal growth stops and not before, provided the joint has been used normally.

This means that the high degree of functional differentiation of joint cartilage is gradually attained during postnatal life; in other words, it is exclusively the use of the joint which brings about the mature architecture of the adult joint cartilage. Without normal function, joint cartilage either disappears entirely or fails to acquire functional structure. It may survive and even proliferate, but such survival and proliferation occur only according to its inherent properties of growth and not according to functional or static demands. The structure will be irregular and without the striking economy displayed by tissues under the influence of function.

Joint cartilage can in a general way be considered that portion of the cartilaginous epiphysis which escapes ossification. It covers the bony epiphysis along a surface which even in adult life shows most of the histologic characteristics of the process of enchondral ossification. There is a layer of calcified joint cartilage corresponding to the zone of provisory calcification, and there is a subchondral bony lamina which takes

the place of the primary spongy bone as soon as the active process of enchondral ossification comes to a standstill. Although the enchondral ossification along the lower surface of the joint cartilage is of little intensity when compared with the ossification along the diaphysial side of the epiphysial plate, it is nevertheless, as I shall show later, of considerable importance for the definite shape of the bony epiphysis.

What is commonly called joint cartilage is only its noncalcified portion. It is by far thicker than the calcified layer and is especially thick in children because the bony epiphysis has not yet enlarged fully at the expense of the proliferating cartilaginous cap. Here, within the noncalcified layers, the gradual development of a static structure can be observed. In infancy the distribution of the cartilaginous cells is irregular. The cells are small, spindle shaped and arranged crisscross in the soft hyaline ground substance, the water content of which is high. This inherited structure, which still resembles the cartilage of embryonal extremities, is gradually replaced under higher differentiation of the cells and consolidation of the hyaline ground substance.

A mature weight-bearing joint permits distinction of three zones in its noncalcified cartilage, the morphologic manifestations of adaptation to intrinsic function. The more superficial cartilaginous layers show small flat single cells distributed parallel to the joint surface, often looking like fibrocytes. The collagenous fibers which make up a considerable part of cartilaginous tissue also run horizontally in this zone. They are hidden in an eosinophilic hyaline ground substance, and they can be made visible only by certain preparations. This superficial layer, which is relatively thin, is the gliding layer (Erdheim), or the tangential zone (Benninghoff). Below it is the middle zone, or the layer of passage, with rather irregular distribution of somewhat larger, spherical cartilaginous cells, which may form smaller cell groups and which lie within a slightly basophilic hyaline ground substance. The main part of the noncalcified joint cartilage is formed by the pressure layer (Erdheim), or the radial zone (Benninghoff). This zone shows elongated cartilage cells grouped together in radial direction and surrounded by a strongly basophilic hyaline ground substance. The cells and cell groups become larger and more nearly spherical the closer they are situated to the calcified layer of joint cartilage. This is in part an expression of the functional structure (pressure is best met by these big cell balls); in part, however, it is a reminiscence of a zone in which proliferation of cartilage occurred during the active stages of enchondral ossification. The collagenous fibers within this zone run perpendicular to the calcified layers, where they are firmly anchored. On reaching the superficial layers they make a sharp turn and run parallel to the joint surface until they reach the margin of the joint, where they again merge into the

deepest calcified layers. It is clear that by this firm fixation of the collagenous fibers within the calcified and the elastic noncalcified hyaline ground substance the joint cartilage is well fitted to receive pressure. The expressions "gliding layer" and "pressure layer" themselves suggest that gliding and pressing motions influence the structure of joint cartilage.

I do not intend to give here a detailed review of the literature concerning the structural adaptation of joint cartilage to function. I wish only to mention Benninghoff's conclusive analysis, which revealed the importance of shearing stresses as true functional stimuli of joint cartilage. Experimental work on animals to study the influence of lasting pressure on joint cartilage has been done by W. Müller and by Koch. An excellent histologic study of human material has been made by Scaglietti.

The cartilaginous changes resulting from disuse are generally better known than are those resulting from pressure. The fact that joint cartilage prospers best if it is treated badly (Fick) suggests that long-lasting periods of rest and exclusion of functional stimuli must lead to alteration of the structure of cartilage. This observation can be made over and over again. Joint cartilage disappears over areas which have lost contact with their antagonist; it remains preserved over the surfaces in contact. Deformed joints, with limitation of motion, changes in the joint axis and in the configuration of the joint ends, dislocated joints and joint ends following exarticulations—all these demonstrate that joint cartilage degenerates and is replaced by fibrous tissue if it lacks contact with its antagonist. Immobilization alone which permits good contact of the articular surfaces with each other, i. e., persistence of some pressure, has proved in many observations not to be greatly damaging to joint cartilage (Reyher, Moll and W. Müller). The peril of immobilization does not threaten so much the joint cartilage as the soft tissues around the joint, especially the joint capsule, shrinkage and adhesions of which may result in stiffness of the joint.

From all these observations it follows that joint cartilage is in constant need of the stimulus of function for the acquisition of a mature structure as well as for its preservation. Unphysiologic demands, i. e., overuse and disuse, are met by degeneration and resorption of joint cartilage and replacement by fibrous tissue. Most of the data (except those of Scaglietti and Rosi) collected from the literature concern cases in which the joint cartilage suffered from disuse or overuse at a time when it had already reached structural maturity or in which great attention was not paid to this question. I give here the analysis of a case in which both factors, disuse and overuse, were working on joints almost continuously for eighteen years after birth. It will be of special interest

to study the influence of alteration of function not only on the cartilaginous cover but also on the shape of the growing joint ends.

REPORT OF A CASE

The patient was a youth aged 18, with spastic quadriplegia and athetosis. The condition had been present since birth. The delivery had been difficult, but it was not known whether forceps had been used. The patient had never talked or walked. He was able to sit in a wheel chair and to feed himself. He had convulsions frequently, with stridor and severe cyanosis. He had no sense of balance; his head dropped forward. There was athetotic motion of the fingers and wrists. The lower extremities were kept adducted most of the time, with flexion contractures of the hips and knees. There was calcaneovalgus of both feet. Occasionally the patient straightened his knees somewhat, which motion was always accompanied by increased calcaneus position of the feet. There was rigor of all the muscles, more noticeable in the upper half of the body. Incontinence of the bladder and the bowel was also noted. The reflexes were pathologically increased. The patient died of cachexia. Autopsy revealed chronic pulmonary tuberculosis, old tuberculous peritonitis with adhesions between the abdominal organs, tuberculosis of the biliary ducts, hemosiderosis of the spleen and brown atrophy of the liver. The brain at gross inspection appeared normal. General severe cachexia was observed.

When the knee and ankle joints were examined anatomically, a considerable range of passive motion was present. Both sides of the body showed essentially the same changes; therefore, description will be given for one side only. The joints were removed unopened from the cadaver. Formaldehyde was injected into the vessels and the capsule was opened after fixation. The exact topographic relation was thus maintained.

Knee Joint.—The lower end of the femur was shaped unevenly; its transverse diameter was relatively much longer than its anteroposterior diameter. The most striking observation was extensive erosion of the joint surface around the intercondyloid notch, involving mainly the cartilaginous cover of both condyles. The defect of the medial condyle was sharply outlined; the margins of the joint cartilage appeared as though punched out. The denuded area was covered by fairly dense connective tissue, through which the underlying hyperemic bone was shining with bluish stain. The defect of the lateral condyle seemed to be denuded entirely, and the cartilage margin looked as though it had been produced artificially. The joint cartilage surrounding the defect was thin, and because of its thinness the hyperemic subchondral bone made it appear blue. The facies patellaris femoris was in firm contact with the patella, and both cartilaginous contact surfaces were free from erosion. However, where the joint surface of the femur was not covered by the patella, there immediately began the great defect that enlarged into the intercondyloid notch. The superior border of the patella likewise revealed absorption and retraction of the joint cartilages, again in an area which was out of contact with the joint surface of the femur. It thus became clear that the huge area of erosion of cartilage was caused primarily by lack of contact between the joint ends. It represented a form of atrophy from disuse.

The medial semilunar cartilage was much smaller than the lateral, but both were free from pathologic change. After removal of the semilunar cartilages, one found that both condyles of the tibia were of even size and the medial condyle was not, as is normal, larger. The portions of the joint surface which had been

covered by the meniscuses revealed a thin joint cartilage of bluish transparency, whereas the central area, which was in contact with the joint cartilage of the femur, showed a thicker, white and opaque cover. These two different portions were separated by a cartilaginous crest, especially on the inner condyle. Such a separation is absent in a normal joint. Both intercondyloid tubercles, lying opposite the extensive eroded area of the femur, also showed thinned-out joint cartilage of bluish transparence.

Ankle Joint.—The right foot was kept in an extreme calcaneus position, which was a little less marked on the left than on the right. The lower joint surface of the tibia showed a number of changes, most of which were due to retraction of the joint cartilage from the margins. Between the articulating surface of the

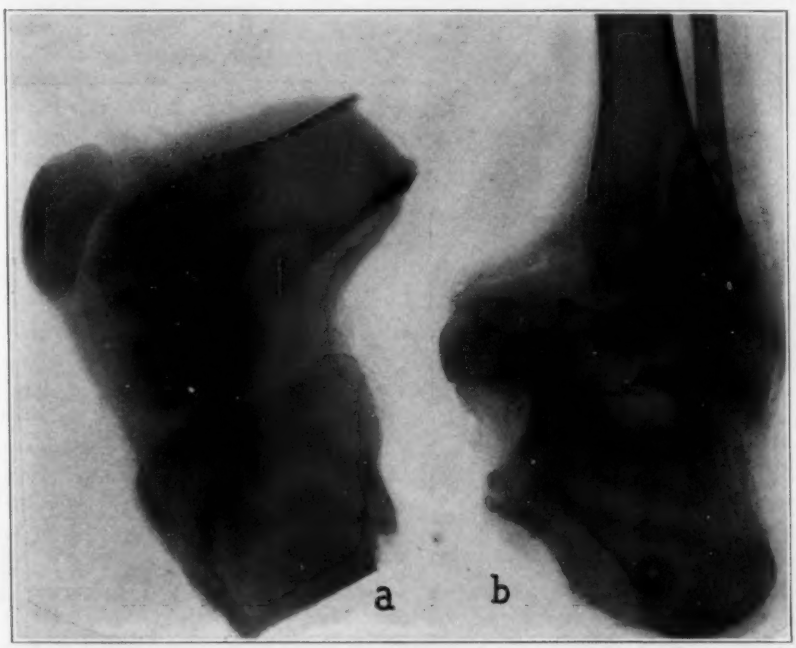

Fig. 1.—Joints of an 18 year old idiot with spastic articular contractures. *A,* lateral view of the knee joint with flexion contracture and slight posterior subluxation of the tibia. Note the reenforced bony trabeculae in the upper end of the tibia, below the contact surface. The epiphysial plates are in beginning occlusion. *B,* lateral view of the ankle region. Note the marked calcaneus position with lines of stress going from the lower end of the tibia through the posterior portion of the astragalus into the tuber ossis calcis. Pressure atrophy of the posterior portion of the body of the astragalus and elongation of the neck may be noted.

thinner malleolus and the outer part of the joint surface there was a large area in which the joint cartilage was entirely absent. Similar smaller areas were also present at the anterior margin of the joint, but in this region they did not involve the entire thickness of the cartilage. The lateral portion of the joint surface which faced the fibula was covered by a thin connective tissue pannus,

EXPLANATION OF FIGURE 2

Black and white drawings made from histologic sections of a pathologic joint compared with corresponding areas of a normal joint of the same age.

A, longitudinal sections through the body of the astragalus. Section *1*, from the idiot with spastic paralysis, is compared with the normal control (*2*). The letter *a* designates the neck of the astragalus; *b*, the anterior portion of the upper joint surface with good joint cartilage of normal thickness; *c*, the posterior joint surface of the subastragaloid joint; *d*, the eroded area of the joint with flattening of the astragalus. The dotted line indicates the loss of osseous epiphysial substance due to the continuous pressure from the side of the posterior joint capsule and the tight tendon of the flexor hallucis longus muscle. Note the difference in the arrangement of bony trabeculae; they are very dense in the subchondral regions of the normal joint, running from the superior joint surface of the subastragaloid joint in the spastic joint.

B, sagittal sections through the posterior margin of the inner condyle of the tibia. There is marked osteoporosis in that from the idiot with spastic contracture of the joint (*1*), with persistence of the epiphysial plate, and the joint cartilage (*a*) is thinned out from below and retracted from the joint margin.

C, sagittal sections through the facies patellaris femoris. Compare that from the spastic joint (*2*) with the normal (*1*). Section *3* is from the outside of the facies patellares. Note the thinning of the joint cartilage where the femur was without contact with the patella (*3*) and the normal thickness where it was in contact (*2*). Note the erosion of the joint surface toward the intercondyloid notch (*1*) with extreme osteoporosis at this area. An epiphysial plate is observed in the section from the spastic joint with dense cancellous bone at its diaphysial side.

D, frontal sections through the medial condyle of the femur; *1* is from the spastic joint; *2*, from the normal control. Note the extreme osteoporosis and deformity. The dotted line shows the great defect of the epiphysis around the intercondyloid notch where the joint cartilage has entirely disappeared.

E, sagittal sections through the patella of (*1*) the idiot with spastic joint contracture and (*2*) the normal control. There is relatively little difference, owing to the fact that in each case the patella was in constant contact with the femur.

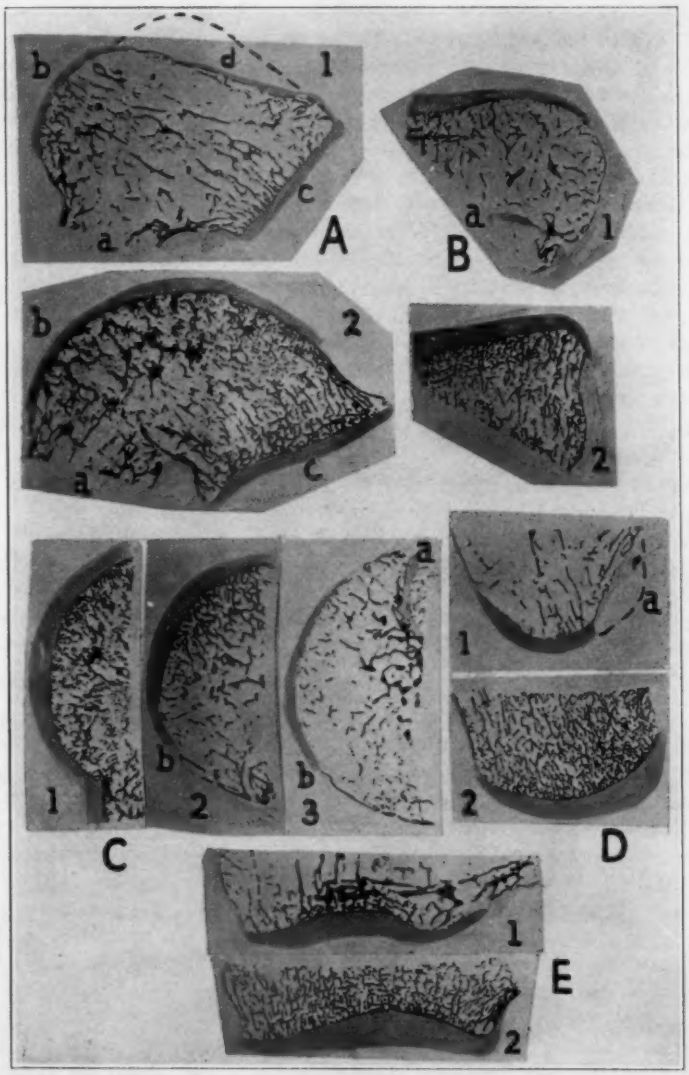

Figure 2

through which the spongy bone showed. The lateral malleolus revealed less marked changes, consisting mainly in retraction of the joint cartilage at the posteroinferior and anterosuperior joint margins.

Astragalus.—The astragalus showed the most changes on its superior joint surface. There was an extensive defect in the joint cartilage, involving more than the posterior half of the joint surface. The cancellous bone was so denuded that it seemed as if a whole sector of the upper part of the astragalus had been cut away. It was evident that this alteration of shape had been brought about by maximal dorsiflexion of the foot, which brought the posterior portion of the astragalus out of contact with its joint surface of the tibia and exposed it at the same time to pressure from the side of the overstretched posterior joint capsule and the tendons of the flexor hallucis longus muscle—a paradigm of erosion of cartilage purely by pressure. The anterior portion of the joint surface showed wider extension than is present under normal conditions, and the neck of the astragalus appeared elongated. In this region the joint cartilage showed another deep erosion into the spongy bone. The defect was covered by fibrous tissue. All the other changes of the astralagus were of minor importance. Corresponding to the defect of the posterior body, both joint surfaces, with the malleoli, were smaller than normal.

Os Calcis.—The os calcis showed relatively mild changes of its joint surfaces. Only the posterior portion of the subastragaloid joint revealed more extensive retraction of the joint cartilage where it was entirely out of contact with the astragalus. The anterior part of the subastragaloid joint was well preserved; it seemed even larger than normal.

The right knee joint, the right tibioastragaloid and the subastragaloid joints were examined histologically. Sections from various parts of the joint ends (fifty-one different places) were studied and compared with corresponding sections from the joints of a normal person of the same age.

Summary.—The detailed histologic reports may be summarized as follows:

The joint cartilage over disused portions rarely reached half the normal thickness. As a rule, it was even much thinner and lacked entirely a functional structure. The whole cartilaginous layer had preserved its embryonal or infantile structure, which means that there was no differentiation into the three typical zones. The cells were not arranged in cell groups. They were spindle shaped or even starlike, densely put together in a hyaline ground substance, which appeared rather soft and even in its deepest layers did not show strong basophilia.

Different histologic pictures were observed at the joint margins. The simplest alteration was that of a gradual thinning out of the joint cartilage. It lost its basophilia entirely and resembled dense fibrous tissue rather than cartilage. Finally it disappeared, and the joint surface was represented by a thin bony lamina covered by some fibrous tissue.

A common finding was the following: The structure of the joint cartilage over the disused portions changed considerably. Besides becoming thinned out, it showed pink-red superficial layers having the appearance more of fibrous than of hyaline cartilage. The cells of the deeper layers were much closer together, so that at first it appeared as if proliferative changes had taken place. The cartilaginous cells formed relatively large balls with three and four nuclei. Frequently the dark blue protoplasm showed signs of mucoid degeneration, especially in the more central layers, which then lost the strong basophilia and appeared silklike. The nuclei also were dark and small, frequently pyknotic. There was

little difference in size between the nuclei in this entirely pathologic area and the nuclei in neighboring areas. The severely degenerated cartilaginous cells were surrounded by halos of ground substance that was much darker blue than is a normal pressure layer. The ground substance, however, was free from signs of degeneration. The distribution of cells in the ground substance was relatively irregular but very dense, so that the proportion of ground substance to cell groups was relatively even. This gave at first view the impression of cellular proliferation, because in a normal pressure layer the proportion of ground substance to cell groups is by far in favor of the former. The actual number of cells and cell groups in this thinned-out cartilaginous portion was as a rule not increased. Only some of the cell groups had enlarged by proliferative activity before they were affected by mucoid degeneration of the cell protoplasm (degenerative hyperplasia).

Most of the cells, however, were simple forms of involution that did not permit differentiation between nucleus and protoplasm. It was clear from these pictures that the marginal portions of the joint cartilage (which under normal conditions are the most active parts and compensate by their proliferation for the daily wear of the superficial cartilage layers) after a short stage of degenerative proliferative activity underwent involution.

This articular cartilage, degenerated by disuse, became resorbed from the joint margin. Different ways of resorption could be observed, the most common being the disappearance of joint cartilage under a fibrous tissue pannus. The pannus could frequently be traced to the synovial fibrous tissue at the margin of the joint; it covered the marginal portion of the joint cartilage for some distance. Typically, the cartilage disappeared incompletely under this pannus, as has been described by Weichselbaum and Pommer. The hyaline ground substance vanished first, thus rendering visible the collagenous fibers which it had previously hidden entirely. The fibers resisted resorption and formed a network, in the meshes of which lay the free cartilaginous cells. Wherever a cartilage cell or cell group became opened after removal of ground substance on one side, a sharply lacunar outline in the hyaline ground substance resulted.

As soon as and sometimes even before the cartilaginous cells were freed from the ground substance, cellular proliferation started. Increasing in number, the cartilage cells changed their character and appeared as simple fibrocytes. In many places it was evident that they participated actively in cartilage resorption by enlargement of their own cell capsules and by phagocytic resorption of the surrounding ground substance.

In the first stages this incomplete process of cartilage resorption sometimes presented itself under the picture of Weichselbaum's lacunae. Later the lacunae enlarged and merged, and then there remained a lacunar irregular upper surface of the joint cartilage. With higher power magnification one was always able to demonstrate that the loose network of collagenous fibers immerged into ground substance along the sharp lacunae.

In more advanced stages the joint surface was covered by a loose layer of fibrous tissue which in great part was the product of the incomplete process of cartilage resorption with transformation of cartilaginous tissue into fibrous tissue. This is important because it shows that a fibrous tissue pannus on the joint surface is not necessarily of synovial origin but may be the direct product of incomplete resorption of cartilage.

Gradually the entire degenerated cartilage disappeared, and the primarily loose fibrous tissue became denser, shrunk and finally covered the subchondral bony lamina in the form of a thin but dense fibrous layer.

The osseous subchondral lamella, here and there, was still in connection with small islands of the zone of calcified cartilage, a sure sign that the old osseous lamella was still present. To prevent an opening of the marrow spaces, it had become reenforced, and compared with the other highly porotic bone tissue of the epiphysis it was of considerable thickness. The surface of the denuded bony lamina was sharply lacunar, and the dense fibrous tissue pannus, close to the bone, showed loosened texture and resembled a cambium layer. In some areas, where resorption from above was quiescent, several small spots of fibrous osteoid tissue were present under the cambium layer.

It was surprising how sharp, as a rule, was the division line between the used and the disused portions of the joint surface. At gross inspection it was characterized by the sharp, punched-out outline of the retracted joint cartilage. This line of retraction was indicated by the amount of articular excursion in a still movable joint or by the extension of the contact surfaces in a firmly contracted joint. In the latter case, joint cartilage with a rather good functional structure ended rather sharply along a line from which the dense fibrous tissue pannus descended almost at right angles to reach the subchondral bony lamina. Such sharp demarcation best illustrates the dependence of joint cartilage on function. It also shows how circumscribed is the action of the preserving functional factors in joint cartilage.

In areas in which the margin of the joint was covered by vascular fibrous tissue, the origin from synovial fibrous tissue was undoubted. The changes in the joint cartilage were then somewhat modified. Owing to the presence of the synovial pannus, the circulation of nutritive fluids in the joint cartilage was increased far above normal. For this reason the superficial cartilaginous layers appeared slightly swollen by edema of the ground substance and, as a good demonstration of the softening of the joint cartilage, "pseudo-structures" (Schaffer) were present in the form of many sharp lines running parallel to the joint surface. The edema of the cartilage accompanied loss of the basophilia of the ground substance. In these regions were found also the proliferative changes of degenerated deep cell groups, which were the result merely of the greater afflux of nutritive substance through the well vascularized pannus.

COMMENT

It is of interest that exactly the same process of removal of cartilage as was present over areas in disuse occurs in areas where remnants of the embryonal cartilaginous cover of the bony epiphysis become superfluous after the definite joint surface has formed. This process did not represent pathologic disuse of the joint cartilage so much as it did physiologic retraction of joint cartilage from the joint margin. Such parts of the epiphysis as, for instance, the posterior portions of the condyles of the tibia, had never been in contact with the antagonist.

In an early stage the histologic picture of this normal resorption of cartilage consists in formation of small holes by resorption of hyaline ground substance around the deeper cartilaginous cells, a picture which is essentially the same as that in the formation of Weichselbaum's lacunae. The difference consists only in the fact that Weichselbaum's lacunae form in the more superficial layers of joint cartilage and, as a

rule, at a greater age, when they belong to the typical picture of degenerative arthritis. The lacunae in physiologic resorption of cartilage form in the deeper cartilaginous layers and are evidently dependent on nearby

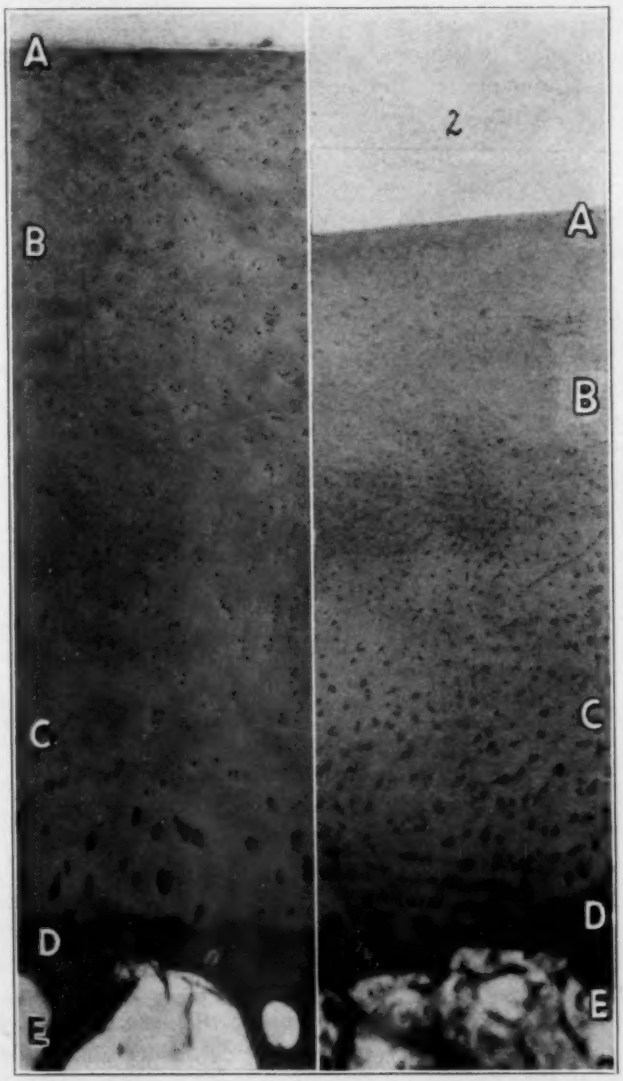

Fig. 3.—Medial condyle of the femur. The normal condyle (left) is compared with that of the idiot with spastic joint contracture (*2*) in the same magnification. There is mature functional structure of joint cartilage in the normal joint. *A* indicates the tangential zone; *B*, the zone of transmission; *C*, the deep pressure layer; *D*, the zone of calcification and subchondral bony lamella; *E*, subchondral bone marrow spaces. The differentiation in these different layers is not so distinct in the pathologic joint, the joint cartilage of which is much thinner despite the fact that there is still active enchondral ossification from below.

marrow spaces. The lacunae may enlarge, merge and form greater areas of fibrous tissue lying in hyaline cartilage. The margins of these cartilaginous defects are sharply outlined if the removal of ground substance is incomplete. The cartilage in which such physiologic resorption takes place entirely lacks basophilia even in its deepest layers, and there is no tendency to form large balls of cells as in areas of pathologic disuse. This is the main difference between pathologic and physiologic retraction of cartilage.

Besides the development of these histologic changes in disused joint cartilage, my investigation showed also the influence of infraphysiologic use of the joint surface on the final shape of the joint ends if disuse started early in life. In an adult one can hardly expect great alteration of the bony epiphysis even with extensive loss of joint cartilage by disuse. There may be considerable osteoporosis, but as a whole the subchondral bony lamina will remain preserved. It is different in the case of a growing person. The joint cartilage of a child is relatively and often absolutely much thicker than that of an adult. The bony epiphysis enlarges gradually by enchondral ossification of the joint cartilage. Proliferation of cartilage occurs because of inherited properties and is at least for some time fairly independent of function. Thus it is possible that the contracted joints of a child with spastic paralysis appear normal in the first years of life. Later, however, when function becomes more and more a decisive factor in the development of the joint ends, those portions of the joint cartilage which lack the stimulus of function do not reveal adequate development. The enlargement of the bony epiphysis is not simply represented by resorption and replacement of the deeper layers of joint cartilage, by which process the bony epiphysis enlarges at the expense of cartilage, which becomes thinned out. Enchondral ossification of the cartilaginous epiphysis is also associated with proliferation of the deepest layers of the noncalcified cartilage. This means that resorption and proliferation of cartilage are well balanced, so as to leave, when physiologic osseous growth stops, a portion of the previous cartilaginous cap of the epiphysis in the form of the articular cartilage.

The importance of function to the cartilaginous structures can be recognized during the first years of postnatal development by the fact that a complex change takes place in the cartilaginous architecture only in joints which are under the stimulus of function. Without function, the cartilaginous cover remains of the same irregular structure with spindle-shaped single cells as is characteristic of embryonal cartilage. It does not show any tendency to acquire a mature functional structure But it also reveals much less proliferative activity of its cells.

One must, therefore, expect that those parts of a growing joint which fall into disuse before the definite normal shape of the joint ends has been reached will remain underdeveloped, because their cartilaginous cover does not keep pace with that of areas which have the stimulus of function. If resorption of cartilage either from above under a fibrous tissue pannus or from below by enchondral ossification is faster than cartilage proliferation, then the entire cartilage cover over the disused portion of the epiphysis will disappear. In a joint which is still growing this loss of cartilaginous tissue is of greater importance than it is in an adult joint. It means that the bony epiphysis which has lost its cartilaginous cover has lost its chance of further increase in size. The joint end will show at this site a defect which cannot be considered a form of simple atrophy from disuse; the condition has followed the lack of enchondral ossification of joint cartilage in the same way as shortening and deformity of an extremity follow premature ossification of an epiphysial plate. The huge defect around the intercondyloid notch in the case which I have described was mainly due to the precocious complete disappearance of joint cartilage over this wide area which was out of contact with the tibia.

This shows clearly that enchondral ossification at the lower surface of the joint cartilage is of great importance for the final shape of the joint ends. Although intrinsic factors, such as heredity, have to be considered first, function, with its definite influence on the growth of the cartilage, is of almost equal value. Physicians have learned to recognize the modeling influence of function on the shape of the long bones. It is known that deranged muscular action may produce osseous deformities. Such deformities develop by direct action on the bony part of the skeleton, the more readily the younger the person (Wolf's law of transformation of bone). My present investigation has shown that deformities in growing persons are not necessarily due to primary disease of the bony epiphyses but are the result of impaired growth of their cartilaginous covering. Early acquired articular contractures, as in my case of the idiot with spastic paralysis, or, even more, congenital deformities in which imbalance of musculature exists, such as congenital clubfoot, bring certain areas of the articular cartilages out of contact and to disappearance. The corresponding areas of the bony epiphysis are affected secondarily. They remain underdeveloped because they have no chance to enlarge by enchondral ossification.

However, it is not always the loss of enchondral ossification which accounts for the deformity of the bony epiphysis. Sometimes it is, on the contrary, hyperactivity of enchondral ossification. In the case described, this was evident along the posterior margins of both condyles

of the tibia. While in the normal control the joint cartilage extended evenly to the posterior border, in the joint with spastic contracture it was thinner, and the posterior portion of the epiphysis formed a steplike deviation. Histologically, the joint cartilage over this area lacked entirely a functional structure. It showed the typical picture of joint cartilage in disuse. It was clear that the pronounced flexion contracture of the knee joint with the slight posterior subluxation of the tibia had brought the posterior portion of the condyles into disuse. Although there was formation of Weichselbaum's lacunae in the superficial cartilage layers, the resorption from above was by no means marked. It certainly could not account for the thinning out. It rather seemed that the marginal portion of the joint cartilage degenerated under the influence of disuse and, being incapable of cellular proliferation, became slowly thinned out by resorption from below according to the process of enchondral ossification. The latter, almost in the same way as it enlarged the bony epiphysis, reduced the thickness of the joint cartilage.

The question is why in some places the epiphysis increases in size at the site of inactive joint cartilage while in others it remains smaller. The reason lies in the stage of development at which the cartilage is put out of function. Around the intercondyloid notch, for instance, the cartilage was probably never under the stimulus of function; therefore it disappeared early, leaving the huge defect of the epiphysis. The posterior portions of the tibia, however, came out of contact with the femur later, when the posterior subluxation developed which in contracture of the knee joint is a later complication. Before this happened, this very portion was in contact with the femur, probably under considerable pressure. Released from this pressure, the joint cartilage underwent all the characteristic histologic changes attributable to disuse, but the enchondral ossification from below became more active and led to the steplike bony prominence of the epiphysis. From the investigations made by Scaglietti, Rosi and Müller and Jores it is known that pressure on cartilage is a retarding and may even become a hindering factor in enchondral ossification. In the case observed by Scaglietti, at the pressure area there was an arrest of enchondral ossification not only of the joint cartilage but also of the epiphysial plate. The animal experiments of Jores and Müller showed the same result except that they revealed also that release from pressure was a new stimulus to growth.

At the contact surfaces, the development of the joint cartilage in the patient with spastic paralysis compared favorably with that in the normal person as to thickness and functional structure. Especially the joint cartilage of the patella and facies patellaris femoris was remarkably mature, and its thickness over the lateral portion was relatively greater

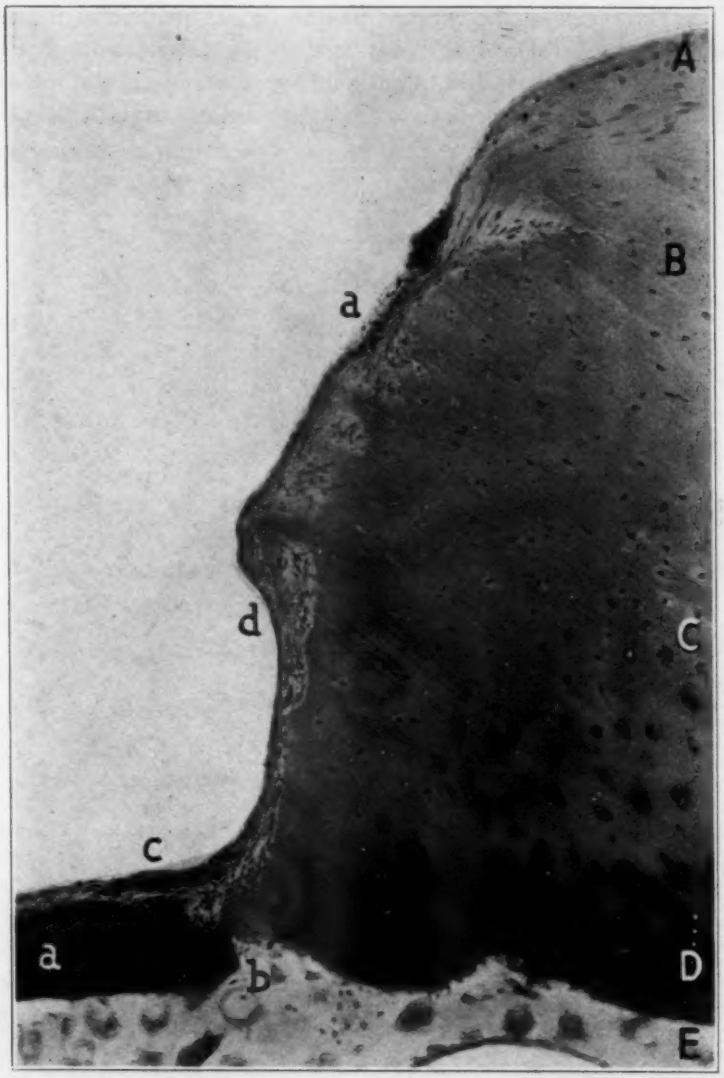

Fig. 4.—Margin of joint cartilage toward intercondyloid notch (facies patellaris femoris). This is the typical picture of "retraction" of joint cartilage. There is good functional structure at the site of contact with the patella. *A* indicates the tangential zone; *B*, the zone of transmission; *C*, the pressure layer; *D*, calcified cartilage with subchondral bony lamina; *E*, serous atrophy of subchondral bone marrow. The joint cartilage ends rather sharply along a line where the hyaline ground substance disappears under preservation of the cartilage cells, which change to fibrocytes and lie between the exposed collagenous fibers. A fibrous tissue pannus (*d*) results, covering the eroded joint cartilage and the exposed subchondral bone (*a*).

than in the normal control. There is no doubt that this extreme development was the result of the continuous pull of the quadriceps muscle on the patella, which pressed it firmly against the lateral condyle of the femur. This pressure effect approximated the physiologic optimum. Degenerative changes were beginning in the joint cartilage of the patella.

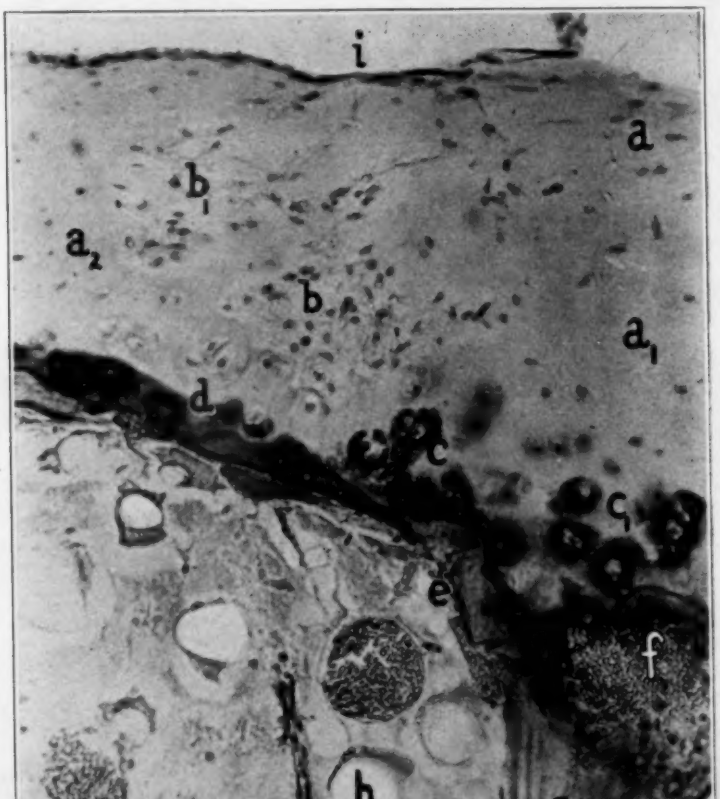

Fig. 5.—Joint cartilage over a disused area of the patella. *a* and a_1 indicate hyaline joint cartilage with cells in very irregular arrangement and with complete loss of normal basophilia; a_2, remaining fields of hyaline ground substance, which at *b* and b_1 disappears, exposing the collagenous fibers and fibrocytic elements. The joint cartilage becomes thinned out and is covered by a thin layer of fibrous tissue, which resembles synovial endothelium. *c* and c_1 indicate irregular calcification around the deeper cell groups (*d*), more diffuse in the ground substance; *e*, apposition of bony tissue over the lacunar surface of the calcified cartilage; *f*, vascular resorption; *g*, subchondral spongy bone; *h*, serous atrophy of fatty bone marrow.

with fibrillation of the superficial layers. These certainly were due to overuse of the joint cartilage. Although the pressure per se did not reach pathologic intensity—on the contrary, for some time it was most favorable to the development of thickness and functional structure of the joint cartilage—it became a damaging factor because of the long period during which it was acting almost continuously. I shall come back to this point a little later.

The joint cartilage over the head of the astragalus was absolutely thicker than the normal. It is certain that this was not a sign of immaturity, though one is accustomed to find thicker joint cartilages in younger persons. There was fully mature functional structure, despite the fact that some active echondral ossification was still going on (the 18 year old idiot still had open epiphysial plates). Function must have been responsible for this overdevelopment of joint cartilage in the same way as it explained the almost normal thickness of the patellar cartilage. There was

Fig. 6.—Sagittal section through the medial half of the lower end of the tibia: *1*, anterior; *2*, posterior. *A* indicates the eroded and somewhat sclerosed anterior margin; *B*, the compressed portion of the joint cartilage; *C*, joint cartilage under more physiologic functional stimulus, and *D*, thinning out of the joint cartilage due to disuse. There is marked osteoporosis of the lower epiphysis.

a striking difference between the poor cartilaginous cover of the tibioastragaloid joint and the almost normal appearance of the subastragaloid joints and the especially thick cartilage in Chopart's joints. If one considers with Roux and Benninghoff the shear or the tangential displacement of the smallest particles within the joint cartilage as the true functional stimulus of the cartilage, then one must recognize that there was a certain spastic motion in these joints which contributed to the good development of the cartilaginous cover. And as a matter of fact, the spastic contracture of the knee joints was released from time to time, and the straightening of the knees was associated with increased calcaneovalgus position of the feet and with plantar flexion of the toes. Some athetotic motion of the toes was frequent. There can be no doubt that these motions, together with the firm contact of the joint ends, were responsible for the preservation and even more for the excellent development of the smaller joints of the ankle region.

Explanation of Figure 7

Different portions of the joint surface shown in figure 6 at greater magnifications.

A, anterior joint margin with eroded joint surface covered by a thin pannus of fibrous tissue (*b*) which produces some fibrous bone at *b*. At *c* may be seen a small remaining island of old calcified joint cartilage included in relatively dense bony lamina; at *d*, bony trabeculae of rather complex structure with cement and apposition lines; at *e*, advanced serous atrophy of fatty bone marrow. *B*, margin of joint cartilage with pressure damage. Fibrous tissue pannus is seen at *a* extending from the anterior joint margin toward the free joint surface, in communication with the marrow at *b* through a hole in the subchondral hard substances. At *c* loose fibrous tissue is seen, the direct product of transformation of hyaline joint cartilage, which loses basophilia and ground substance at *d*. The deepest layers of the cartilage (*e*) show dense accumulation of dark pyknotic cell groups and irregular junction of the calcified cartilage and the subchondral bone. *C*, portion of the joint surface with fairly well developed functional structure of joint cartilage. There is slight depression of the joint level at *a*, due to the lack of supporting subchondral bone. At this area basophilia is absent and the distribution of cells and cell groups is irregular. The bone marrow borders directly on the joint cartilage, owing either to osteoporosis or to still active enchondral ossification. *D*, joint cartilage which under functional stimulus becomes rapidly thinned out toward the posterior joint margin. The superficial cartilage later shows absence of basophilia and cells which resemble fibrocytes; the deeper layers show very dense accumulation of round dark blue cell groups, involution forms. A thin pannus of fibrous tissue is present on the surface at *a*. There is extreme osteoporosis, with denudation of the lower surface of the joint cartilage for long distances.

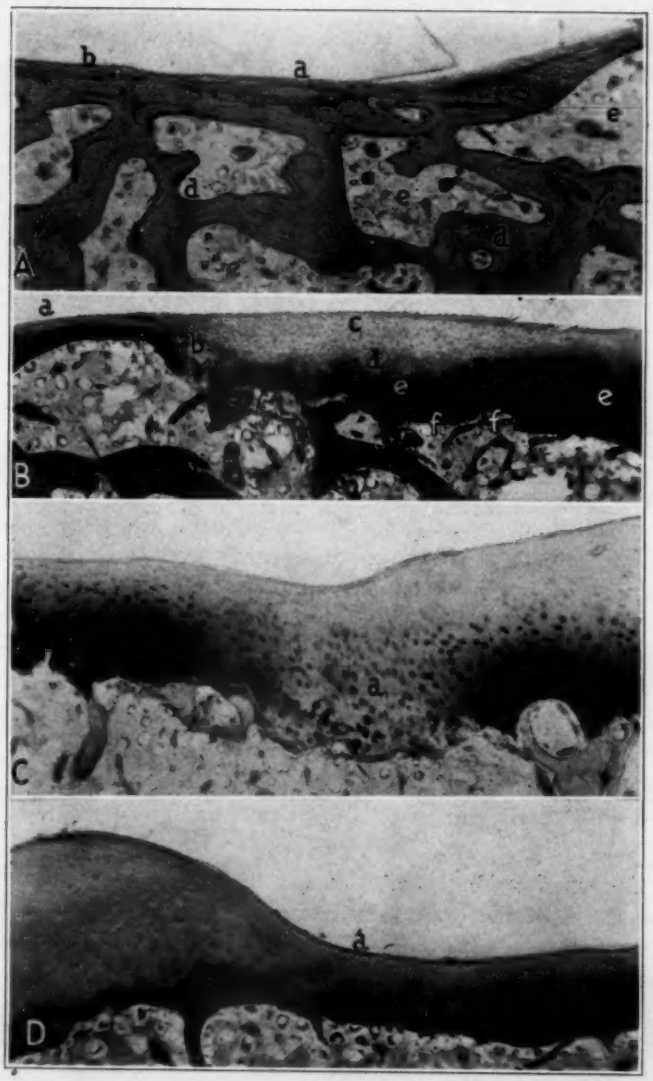

Figure 7

I shall now discuss those articular portions in which joint cartilage meets ultraphysiologic demands. Such places were found in the tibio-astragaloid joint, mainly over the posterior portion of the body of the astragalus but also at the lower surface of the tibia and on both malleoli. Changes due to constant pressure could be studied, from the slightest beginning alteration to the most extensive erosion from cartilage into the subchondral bone. It does not make any appreciable difference histologically whether the damage resulting from compression of joint cartilage was caused by soft tissues, by joint cartilage or by bone. The first changes invariably consisted in a thinning out of the joint cartilage at the point of increased and continuous pressure. This thinning was evidently due to a loss of fluids from the ground substance. It led to complete loss of normal basophilia and to denser arrangement of the cells. With the loss of fluids from the ground substance, the nutrition of the tissue was impaired, and necrosis of cells was common.

The best illustration of pressure damage to a joint was given by the astragalus, the body of which was extremely deformed. It was flattened by the maldevelopment of the posterosuperior joint surface, which presented a large eroded area, a typical pressure sore of joint cartilage and underlying bone. At the posterior margin of the eroded area, joint cartilage was still preserved in a stage which permitted the study of the earlier stages of pressure damage. The joint cartilage was very thin, entirely without basophilia and of pink-red stain. It gave the impression of being of slight consistency. In about two thirds of its thickness the cartilage contained, in loose arrangement, cells which resembled fibrocytes rather than cartilaginous cells. The cells showed horizontal orientation, lying parallel to the joint surface, no doubt as the result of compression. Only in the deepest layers were round cells present; these had the appearance of cartilaginous cells. There were absolutely no signs of proliferation.

The severely damaged cartilage underwent disintegration with resorption close to the eroded area. The resorption took place again according to the incomplete process described by Weichselbaum and Pommer. This process reduced the compressed cartilage gradually to smaller islands and caused its worm-eaten appearance. The smaller pieces revealed necrosis of cells, which could also be seen (but to a lesser degree) in the simply compressed joint cartilage which had not yet undergone resorption.

Resorption of the thinned-out cartilage which by compression alone had become impoverished in substance was mainly from above, either under a fibrous tissue pannus which derived from the joint margin or from the bone marrow of the opened marrow spaces or without occurrence of a true pannus, simply by backward development of

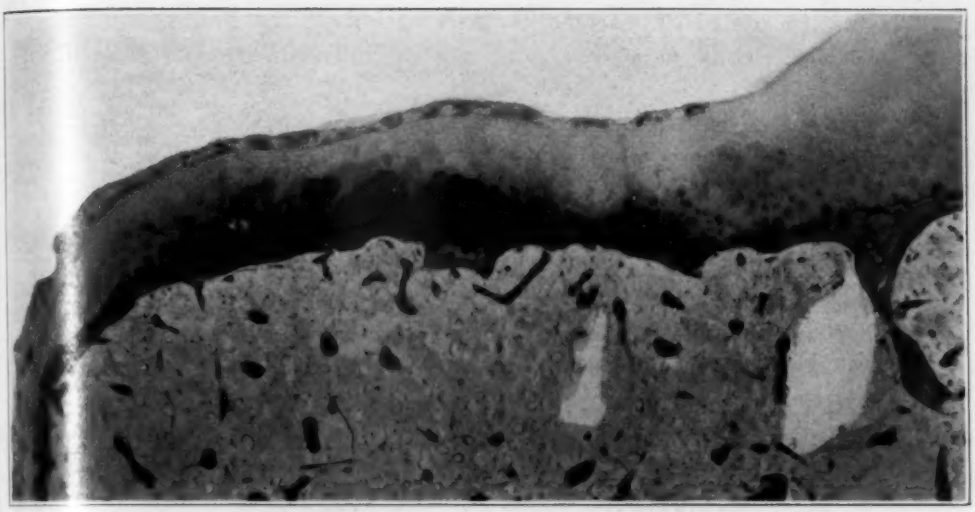

Fig. 8.—Typical picture of changes in joint cartilage, caused by disuse. The lateral portion of the lower joint surface of the tibia is shown. The joint cartilage is thinned out; the superficial layers are bright and the deeper ones dark, owing to dense accumulation of strongly basophilic cell groups. The surface is covered by a fibrous tissue pannus which derives from the joint margin and leads many vessels. There is extreme osteoporosis with serous atrophy of fatty bone marrow.

Fig. 9.—Compressed joint cartilage at the posterior portion of the head of the astragalus. The joint cartilage is thinned out, with complete absence of basophilia of the ground substance, even in the deepest layers. The cells are single and very densely distributed; a good many in the deepest layers are necrotic. Note resorption of the joint cartilage from below by bone marrow spaces which contain vessels and which incompletely remove the cartilage. Note also the serous atrophy of bone marrow.

cartilaginous tissue to fibrous tissue, according to the incomplete process of resorption. The further thinning out of the already compressed joint cartilage was then caused by gradual wasting of the most superficial layers, facilitated by washing or pressing out of the hyaline ground substance. Only in a very small portion did cellular resorption of cartilage by chondroclasts take place.

Compared with the resorption of cartilage from above, that from below by bone marrow was negligible. Only in a very few places could larger bone marrow spaces be noticed extending into the noncalcified and compressed cartilage. In this region also resorption was incomplete and was sometimes preceded by the formation of Weichselbaum's lacunae. Irregular fibrous spaces resulted, in the margins of which typical blending of collagenous fibers from the degenerated cartilage into young fibrous bone marrow was seen. This was a sign that the

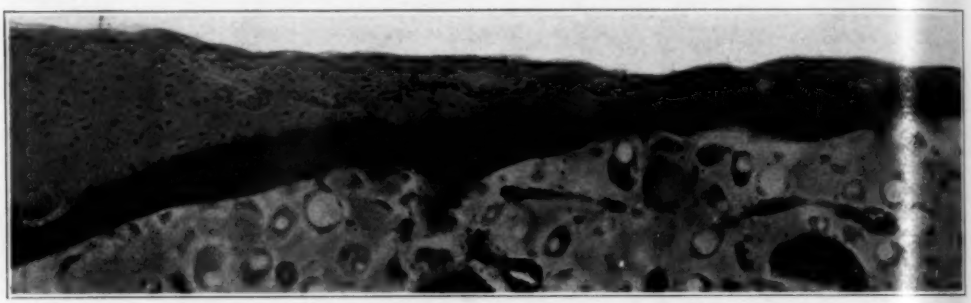

Fig. 10.—Resorption of the compressed joint cartilage of the head of the astragalus. The margin of the wide eroded area is shown. The joint cartilage, free from basophilia and with irregular distribution of its cells, becomes rapidly thinned out toward the eroded area. Loose fibrous tissue remains on the surface, a product of incomplete resorption of cartilage, to which the ground substance yields but which the collagenous fibers resist. The fibrous tissue does not contain vessels.

degenerated and compressed joint cartilage stimulated the subchondral bone marrow to reactive changes which surpassed occasionally the amount characteristic of simple atrophy. The invasion of noncalcified joint cartilage by marrow spaces is, according to the functional theory of Pommer, a characteristic response to the degeneration of joint cartilage, especially to its loss of elasticity. This is considered by Pommer as pathognomonic of arthritis deformans.

It was of interest to observe that over the area in which there was increased pressure a membrane of fibrinous exudate was present, which apparently had connected the joint capsule with the joint surface in the sense of beginning fibrous ankylosis. This was also only the consequence of the constant calcaneus position producing constant pressure and irritation from the side of the tight joint capsule.

The lateral portion of the astragalus also revealed a most interesting condition. The surface in contact with the lateral malleolus showed posteriorly a definite impression involving the cartilaginous cover as well as the bony epiphysis. The anterior portion of the joint cartilage was of good functional structure. It was smooth and revealed a number of necrotic cells more or less in even distribution, as may be expected at this age in a joint on the way to full functional development. Posteriorly, however, where the astragalus was pressed against the outer malleolus, the structure of the joint cartilage was entirely pathologic. Owing evidently to compression, it was thinned out, which resulted in a flat, troughlike depression of the joint surface. There was a very thin fibrous layer on the surface. This corresponded to synovial endothelium rather than to a fibrous tissue pannus and had but little resorptive activity. The structure of the compressed cartilage differed from the clear functional structure of the neighboring areas. For a short distance, limited to the circumscribed pressure, the cells were dense and were irregularly distributed, while a considerable number were necrotic. The cells in the deepest layers were extremely basophilic and showed pyknosis. The number of necrotic cells became larger as one proceeded toward the center of the compressed area. In the lower two thirds of the cartilage were extensive fields of ground substance which showed only shadows of cartilage cells intermingled with dark blue forms of involution—these resisted the removal of chromatin substance longer. The zone of passage apparently was free from cellular necrosis. The nuclear stain was well preserved, but a number of cells revealed slight mucoid degeneration of their protoplasm. The most superficial layers had very dense arrangement of the cells, which were more fibrocytic than cartilaginous.

From this picture it was clear that the damage to the joint cartilage was due to severe and probably persistent pressure. The deeper cartilaginous layers seemed to be more affected than the superficial ones. The changes were in a relatively early stage, and reactive processes had not yet taken place.

In the more advanced stages, as presented by the large eroded area of the astragalus, the fibrous degeneration of joint cartilage was complete; the cartilage gradually disappeared under the picture of incomplete resorption just as it did over areas in disuse. The underlying bone showed the most extreme degree of osteoporosis; there was only a large cystic area filled with cachectic fatty bone marrow. Despite this extreme atrophy of bone, the area of erosion was separated from the marrow by a thin bony lamina which had been displaced considerably toward the center of the epiphysis. This fact alone revealed that the bony lamina was not the old denuded subchondral bony lamina but had been formed during or after the disappearance of cartilage. At the superior surface

of the bony lamina, there was fine lacunar resorption by multinuclear giant cells, and at its endosteal side there was some bone apposition. The combination of both processes brought about the displacement of the bony lamina toward the center of the epiphysis. The bony lamina consisted of mature lamellar bone tissue and was covered by a thin fibrous membrane which permitted recognition of two layers, one superficial, consisting of denser connective tissue with arrangement of its fibers parallel to the joint surface, and the other deeper, vascular, looser and richer in cells. This difference was due only to the difference in mechanical irritation, the deeper layer being more protected. The superficial dense layer may even become necrotic under persistent pressure.

Complete atrophy of joint cartilage through disuse or pressure will lead to deformity of the growing joint ends because of the disturbance of enchondral ossification. The latter will be retarded or stopped during the period that the joint cartilage is exposed to increased pressure; it is rendered entirely impossible after the joint cartilage has disappeared. If the pressure is marked and persistent, it will lead also to resorption of bone after the joint cartilage has disappeared, and thus the deformity of the bony joint end will increase.

However, the same pressure which is too high for the cartilage may form a stimulus to osseous growth and lead to osteosclerosis rather than to pressure atrophy. This was especially the case at the anterior border of the lower joint surface of the tibia. Here the joint cartilage had disappeared completely, and the subchondral bone was denuded. Osteoid or smaller calcified foci of fibrous bone tissue could be observed over more prominent points of the surface. Under the bony lamina, relatively dense spongiosa was present, with many cement and apposition lines. Small islands of calcified cartilage were included not only in the superficial bony lamina but also in the deeper bony trabeculae. This demonstrated conclusively that the whole system of thick bony trabeculae occupied the site of former joint cartilage which had disappeared under the increased pressure. The exposed osseous tissue, however, had increased in density under the same stimulus of pressure, although all the other portions of the tibia showed decided osteoporosis.

In this connection, a few words may be said about the bony joint ends. Extreme osteoporosis was noticed at gross inspection. Corresponding to this but also to the fact that enchondral ossification had not yet ceased, the lower surface of the joint cartilage was most irregular. The zone of provisory calcification was interrupted frequently, so that bone marrow was bordering immediately at the noncalcified joint cartilage. Closer examination showed that calcification was always present where joint cartilage and bone marrow came together. This indicated the great mechanical importance of the calcification, which in great part

is meant as a fortification of the connection between osseous and cartilaginous tissue. In other words, cartilage calcifies where there is a static or mechanical need for calcification (calcioprotective law of Erdheim). Such cases of extreme osteoporosis, in which the calcium-containing tissues are reduced to a minimum, are excellent examples of the dependence of cartilage calcification on mechanical and static stress which, of course, will be greater where there is connection between cartilaginous and osseous tissue.

The condyles of the femur and tibia showed such a severe lack of osseous tissue that there were wide areas occupied only by bone marrow. The few bony trabeculae were without static arrangement and occasionally showed lacunar outlines. They were of surprisingly complex structure, with many blue cement lines. This was a definite sign that despite the lack of static use and the severe degree of osteoporosis the bone tissue had undergone structural changes. It was not a simple process of bone resorption which gradually reduced the amount of bone tissue but, as always with bone atrophy, a rather complicated process of bone transformation, resorption and apposition changed the entire osseous architecture of the epiphysis. In some areas the few bony trabeculae present were thicker than normal; they often showed perforating vessel canals included in thick inner portions which were crossed by many cement lines (sclerosing osteoporosis).

Those portions of the condyles, however, which were evidently under static stress (they were also covered by joint cartilage of almost normal thickness and good functional structure) revealed considerable density of osseous tissue. The posterior portions were even denser than normal. The relative osteoporosis of these parts in the normal person is easily understood. They are in contact with the tibia only in extreme flexion of the knee joint, a position rarely combined with weight bearing. The constant spastic muscle pull in the contracted knee joint of the idiot brought the posterior portions of the condyles of the femur under ultraphysiologic pressure, which prevented and even overcompensated osteoporosis that in all other places had occurred.

A characteristic picture of atrophy of the fat marrow was associated with the pronounced osteoporosis. The wide marrow spaces, which occupied in some places large cystlike areas, were filled with jelly bone marrow, such as is found frequently in cachectic persons. The reticulum of the bone marrow was easily visible, principally because almost all the capillary vessels were engorged. The fat cells at first view seemed to be decreased in number, and the few which were visible were minute. At closer inspection one found, however, that in many places the cell membranes persisted in their normal dimensions; it was the fatty content of the cells which had shrunk and had frequently even become divided

into several smaller droplets. The remaining cell area was occupied by a serous fluid apparently rich in proteins. The protein substance appeared as fine eosinophilic granules. The nucleus of the fat cell was found among these granules or, more commonly, at the periphery, as in the signet ring cell. Between the fat cells, especially in areas in which they became smaller after loss of the fat substance, edema fluid was present. Sometimes large free histiocytes of protoplasmic appearance were seen in the edema fluid.

The whole picture was typical of "serous atrophy" of fat tissue as it can best be seen in the bone marrow of cachectic persons. In contradistinction to the other forms of atrophy of fat tissue, simple atrophy and the *Wucheratrophie* (Flemming), in which the size of the fat cell changes, serous atrophy preserves more or less the normal size of the fat cells; the atrophy concerns mainly the fatty content of the cell, which becomes replaced by serous transudation. In more advanced stages, when shrinkage of the entire cell takes place, halos of edema fluid may be seen around the fat cells, or with complete loss of fat substances the bone marrow may consist only of the remaining reticulum and of edema.

Summarizing, one may say that functional stimuli below or above the physiologic optimum, if active over a long period, are deleterious to joint cartilage. The damage does not remain limited to the joint cartilage in growing persons but draws the bony epiphysis into participation by stopping further enchondral ossification. This point has been entirely neglected by former investigators. They concentrated mainly on the immediate changes in the joint cartilage and attributed more pronounced alterations in the osseous structures simply to atrophy from disuse.

This study of contracted joints revealed also that the time factor is of greatest importance in the development of pathologic changes in the joint cartilages. The pressure force may stay within normal limits; nevertheless, it will damage the joint cartilage if it is active more or less continuously over a long period. The same is true of disuse. Too little or too much use of joint cartilage over a long period is detrimental. This is confirmed by almost every day's operative and autopsy material and does not need proof by animal experimentation. With genu valgum or genu varum, for instance, typically hypertrophic arthritic changes develop in older age. Marginal exostoses and degeneration and fibrillation of joint cartilage will be present at the condyles with increased weight bearing, while atrophy and retraction of joint cartilage are noticed in the condyles with less weight bearing. But even an apparently normal knee joint of an older person will show the dependence of the structure of joint cartilage on function. The joint cartilage of the tibia, for

instance, is different where it is covered by the semilunar cartilage and where it is in free contact with the lower end of the femur. In the former region the cartilage is well preserved and smooth (the only significant point is that it is of the yellow color of senile cartilage, whereas young cartilage is bluish white); over the centrum, however, the cartilage is thinned and rough. The explanation is simple. The central portion of the tibial condyles is in constant contact with the condyles of the femur; pressure and friction are here pronounced, whereas the motion between the meniscuses and the joint cartilage of the tibia is relatively small and permits better preservation of joint cartilage. This difference can be seen even better in genu valgum and genu varum. The central area of the weight-bearing condyle of the tibia may show degenerated, fibrillated joint cartilage, or it may even be denuded and the osseous surface polished and sclerosed, while the marginal portions, covered and protected from too much pressure by the semilunar cartilage, show fairly well preserved joint cartilage.

Whether the pressure force is intense and working over a relatively short period, or whether it is still within physiologic limits but of protracted or even continuous action, the result will be the same: The joint cartilage will lose its normal elasticity and will suffer irreparable damage. Bär found experimentally that the normal elasticity of joint cartilage is impaired considerably by long duration of pressure forces. With the loss of elasticity, the ways are opened for the different processes of cartilage degeneration, even for reactive resorption from below by bone marrow—all changes preceding and accompanying hypertrophic arthritis. One also concludes from this study that there is nothing specific to hypertrophic arthritis or arthritis deformans. Any marked alteration of function for a long period (infraphysiologic and ultraphysiologic demands) is certain to lead to degenerative changes of joint cartilage and may be followed by the whole syndrome of fully developed arthritis deformans, the more probably the longer the joint is exposed to unphysiologic use.

THYROID GLAND: A CLINICAL PATHOLOGIC STUDY WITH SPECIAL REFERENCE TO TRUE TUMOR

ANALYSIS OF TWO HUNDRED AND SIXTEEN CASES

EMIL J. DELLI BOVI, M.D.
Assistant in Surgery
NEW YORK

In spite of the voluminous literature and of present knowledge based on extensive experimental studies of certain morbid changes occurring in diseases of the thyroid gland, there still exist, perhaps as in no other field of human pathology, the greatest differences of opinion and the most widespread confusion. Much of the existing divergence and antagonism in views, however, as well as the conflicting interpretations of the thyroid gland both in health and in disease, undoubtedly can be attributed to incomplete knowledge of the structure and physiology of the gland and to its many physiologic and histologic variations and irregularities. This appears to be particularly true as regards the pathologic significance of benign nodules or tumefactions of the thyroid gland and their relation to states of hyperactivity of the gland.

Such tumors or nodules occurring in cases of nodular goiter were for many years considered distinct pathologic entities and were often termed adenomas or fetal adenomas; that is, they were thought to be true benign neoplasms the activity and growth of which were responsible for the anatomic and functional disturbances occurring in patients with symptoms of hyperthyroidism. It is now, I believe, generally agreed as a result of detailed studies that the thyroid gland is an extremely variable organ, particularly influenced by locality and by physical and chemical stimuli and capable of undergoing marked changes in histologic structure resulting from all degrees of hypertrophy and hyperplasia, from the simplest type observed in puberty and in cases of compensatory hypertrophy to the extreme types observed in cases of exophthalmic

From the Department of Pathology and the Third Surgical Division (New York University College of Medicine, Graduate Course in Surgery) of Bellevue Hospital.

goiter. Rienhoff [1] in 1926, from his studies of the involutional and regressive changes in the thyroid gland following either physiologic or pathologic hypertrophy and hyperplasia, concluded that "these nodules as found in nodular goiter, are nothing more than involutional bodies, the result of an attempt on the part of the thyroid gland, following a period of hyperactivity, to re-approximate its normal histologic structure."

With this in mind, I undertook the task of reviewing and analyzing the results of pathologic examinations of 216 consecutive thyroids surgically removed in cases of hyperthyroidism of varying degree with the purpose not only of presenting a detailed survey of the occurrence of diffuse hyperplasia, nodular goiter and true tumors of the thyroid gland in this series of patients but of properly interpreting and evaluating the pathologic significance of the tumors and their relation to hyperthyroidism. The attempt is based on the extensive studies of Rienhoff and Lewis.[2]

MATERIAL AND METHOD

These specimens consisted of thyroid glands on which partial lobectomies had been performed. They were all fixed in solution of formaldehyde U. S. P. (10 per cent concentration). The series of cases represented by them extended over a period of five years, from October 1930 to October 1935. A few additional cases, although probably authentic instances of these conditions, were excluded, either because the gross material was insufficient or because the reports lacked a suitable histologic description. The gross and microscopic studies were made not on serial sections of the material but on sections of the specimens taken at random, although an attempt had been made to preserve and include all areas of interest for pathologic examination. The gross specimens were inspected with regard to their consistency and translucency and the presence or absence of nodules as seen with the naked eye. The various characteristics of these tumefactions were carefully recorded; that is, whether they were single or multiple, whether they were encapsulated and whether visible colloid or acini were present. When nodules were seen, paraffin sections of the material, stained with hematoxylin and eosin, were reviewed histologically for the purpose of comparative study.

The microscopic examinations took into account the nature of the capsule, the type of nodule, the presence or absence of lymphocytic foci, the follicular epithelium within and without the nodule, the size, shape and contents of the follicles, areas of hyperinvolution or hypoinvolution and the presence or absence of the various sequelae of extreme regression and disintegration, such as fibrosis, hemorrhage, scarring, hyalinization, cyst formation and calcification. In determination of the relation of true benign tumors of the thyroid gland to hyperthyroidism, the clinical histories as well as the pathologic reports and slides were carefully reviewed.

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1. Rienhoff, F. W.: Involutional or Regressive Changes in the Thyroid Gland, and Their Relation to the Origin of the So-Called Adenomas, Arch. Surg. **13**:391 (Sept.) 1926.

2. Rienhoff, F. W., and Lewis, D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928.

ANALYSIS OF DATA

Of the 216 thyroids examined, 139, or 64.3 per cent, showed diffuse hyperplasia and 41, or 19 per cent, nodular goiter. True tumors occurred in 36, or 16.7 per cent. A further subdivision of the third group demonstrated that 25, or 69.4 per cent, were true benign adenomas; 9, or 25 per cent, fetal adenomas, and 2, or 5.6 per cent, carcinomas (table 1). The glands with diffuse hyperplasia were studied chiefly from a statistical point of view, as they presented in practically

TABLE 1.—*Incidence of Diffuse Hyperplasia, Nodular Goiter and True Tumor in 216 Thyroid Glands*

Condition	Number of Specimens	Percentage
Diffuse hyperplasia	139	64.3
Nodular goiter	41	19.0
True tumor	36	16.7
Benign adenoma	25	69.4
Fetal adenoma	9	25.0
Carcinoma	2	5.6

TABLE 2.—*Sex Incidence* of Diffuse Hyperplasia, Nodular Goiter and True Tumors*

	Females		Males		
Condition	Number	Percentage	Number	Percentage	Ratio
Diffuse hyperplasia	100	71.9	39	28.1	2.6:1
Nodular goiter	35	85.4	6	14.6	5.8:1
True tumors	25	69.4	11	30.6	2.3:1
Benign adenoma	17	68.0	8	32.0	2.1:1
Fetal adenoma	7	77.8	2	22.2	3.5:1
Carcinoma	1	50.0	1	50.0	1:1

* The total number of thyroids was 216. Of these, 160 (74.1 per cent) were removed from females and 56 (25.9 per cent) from males.

all instances the gross and histologic picture typical of the various types and degrees of hypertrophy and hyperplasia.

AGE AND SEX DISTRIBUTION

Of the entire series of 216 thyroids, 56, or 25.9 per cent, were taken from males and 160, or 74.1 per cent, from females, giving a ratio of 1 to 2.8. Thirty-nine, or 28.1 per cent, of the thyroids removed from males and 100, or 71.9 per cent, of those removed from females showed diffuse hyperplasia; of the thyroids which showed nodular goiter, 6, or 14.6 per cent, were from males and 35, or 85.4 per cent, from females; and of the thyroids which showed true tumor 11, or 30.6 per cent, were from males and 25, or 69.4 per cent, from females.

From the 36 specimens in the third group, that of true tumors, the following data were obtained: Of the total number of growths, 25 were benign adenomas; 8, or 32 per cent, of these were from males, and 17, or 68 per cent, from females. There were 9 fetal adenomas, of which 2, or 22.2 per cent, were from males and 7, or 77.8 per cent, from females. The 2 carcinomas were equally distributed between the two sexes; of the total number of 216 specimens, the 2 of carcinoma constituted but 0.93 per cent.

A review of the records with regard to age revealed the increasing frequency of diffuse hyperplasia, particularly in women, beginning at puberty and reaching its maximum between the twenty-first and the

TABLE 3.—*Age and Sex Distribution in 216 Cases During a Five Year Period*

Age, Years,	No. of Patients	Diffuse Hyperplasia		Nodular Goiter		True Tumors: Benign Adenoma		Fetal Adenoma		Carcinoma	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
11 to 15	2	0	1	0	0	1	0	0	0	0	0
16 to 20	13	0	8	0	1	1	3	0	0	0	0
21 to 25	28	4	19	0	2	0	1	0	1	1	0
26 to 30	32	2	17	2	4	2	4	0	1	0	0
31 to 35	30	10	19	0	4	2	3	1	0	0	0
36 to 40	24	7	7	1	7	0	2	0	0	0	0
41 to 45	19	4	9	0	5	0	1	0	0	0	0
46 to 50	37	4	15	3	10	1	2	1	1	0	0
51 to 55	14	6	4	0	1	1	1	0	1	0	0
56 to 60	6	1	1	0	0	0	0	1	2	0	1
61 to 65	2	1	0	0	1	0	0	0	0	0	0
Total....	216	39	100	6	35	8	17	3	6	1	1

thirty-fifth year of life, the period of greatest sexual and ovarian activity (menstruation, pregnancy and lactation).

That the physiologic hormonal influence active during this period may be related to hyperactivity of the thyroid is further evidenced by the sudden rise in the incidence of this condition at the time of the menopause. The incidence in men was constant throughout except for a slight rise during early adult life. Nodular goiter was encountered more frequently with advancing age, especially in women, reaching its peak at middle life and occurring infrequently after that. It was uncommon in persons below 15 years of age. Benign adenomas and fetal adenomas and the 2 carcinomas appeared equally distributed in the two sexes throughout early and late adult life. The younger patient with carcinoma of the thyroid gland was a man 22 years of age. The second carcinoma occurred in a woman 60 years of age (table 3; charts 1 and 2).

A review of the obstetric histories in the 216 cases demonstrated that practically every one of the pathologic states of the thyroid gland was more prevalent in parous than in nulliparous women, occurring roughly one and one-half times as frequently. For benign adenoma the converse was true (table 4).

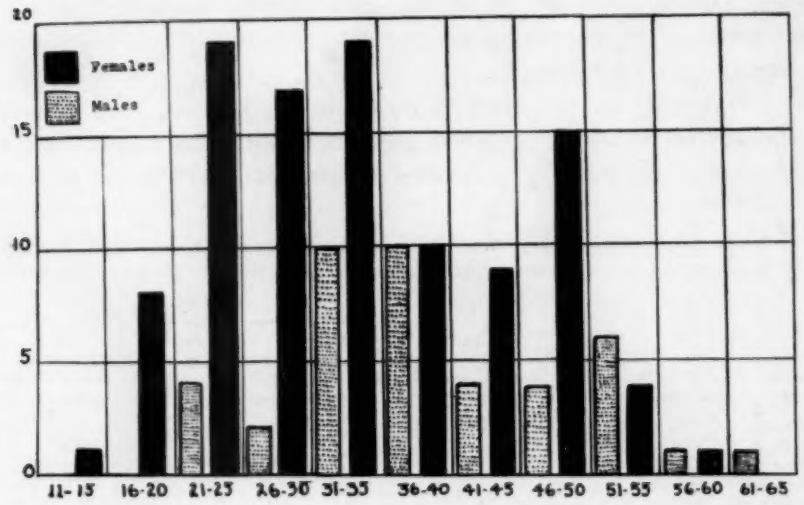

Chart 1.—Age and sex incidence of diffuse hyperplasia during a five year period.

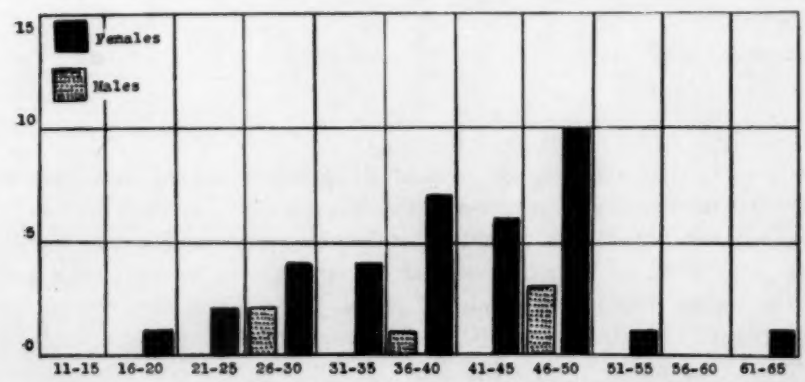

Chart 2.—Age and sex incidence of nodular goiter during a five year period.

From the foregoing facts it would seem reasonable to conclude, in spite of the preponderance of diffuse hyperplasia, that nodular goiter and true tumors occurred with almost equal frequency, although the benign adenomas by far outnumbered both the fetal adenomas and the carcinomas. Whereas nodules were encountered six times more often in women than in men, true tumors of the thyroid gland occurred only twice as often in women.

INCIDENCE OF NODULES

Clerk,[3] of Berne, Switzerland, found nodules in more than half the thyroids of the persons over 20 years of age whom he studied and in practically all the thyroids of those past middle life. Wegelin [4] observed tumefactions in 73.3 per cent of the men and in 88.4 per cent of the women past 20 years of age in his series, while Klöppel,[4] of Freiburg, Germany, reported nodose goiters in 81 per cent of persons past middle life. Wilson [6] found diffuse hyperplasia in 79 per cent of his cases and adenomatous nodules in 21 per cent.

Jaffé, in the Chicago region,[7] found nodules in the thyroids of 30 per cent of the males whom he observed and in 44.7 per cent of those of the females. Rice,[8] in Minnesota, examined 493 thyroids, of both

TABLE 4.—*Incidence of Diffuse Hyperplasia, Nodular Goiter and True Tumor of the Thyroid Gland in Nulliparous and Parous Women*

	All Thyroids Removed from Females (160)		Thyroids Removed from Parous Women (98, or 60.1%)		Thyroids Removed from Nulliparous Women (62, or 39.9%)		
	Number	Percentage	Number	Percentage	Number	Percentage	Ratio
Diffuse hyperplasia	100	62.5	44	64.0	36	36.0	1.8:1
Nodular goiter	35	21.9	21	60.0	14	40.0	1.5:1
True tumors	25	15.6	13	52.0	12	48.0	1.1:1
Benign adenoma	17	68.0	7	41.2	10	58.8	1.1:4
Fetal adenoma	7	28.0	5	71.4	2	28.6	2.5:1
Carcinoma	1	4.0	1	100.0	0	0.0	.....

males and females. He found that nodules were present in 43.8 per cent of all those removed from males and that the same condition existed in 53.1 per cent of those removed from females.

Nolan,[9] also of Minnesota, in a review of 725 thyroid glands removed intact at autopsy, observed nodules in 191, or 26.3 per cent. The 191 thyroids represented a combination of 22 per cent of all

3. Clerk, E.: Die Schilddrüse im hohen Alter vom 50 Lebensjahr an aus der norddeutschen Ebene und Küstengegend sowie aus Bern, Ztschr. f. Path. **10**:1, 1912.

4. Cited by Nolan.[9]

5. Footnote deleted on proof.

6. Wilson, L. B.: The Pathology of the Thyroid Gland, Am. J. M. Sc. **146**: 781, 1913.

7. Jaffé, R. H.: Variation in the Weight of the Thyroid Gland and the Frequency of Its Abnormal Enlargement in the Region of Chicago, Arch. Path. **10**: 887 (Dec.) 1930.

8. Rice, C. O.: The Life Cycle of the Thyroid Gland in Minnesota, West. J. Surg. **39**:925, 1931.

9. Nolan, L. E.: Variations in the Size, Weight and Histologic Structure of the Thyroid Gland, Arch. Path. **25**:1 (Jan.) 1938.

those removed from males and 42 per cent of all those removed from females.

While my statistics on nodular goiter do not show as high an incidence as do those reported by the aforementioned authors, it must be remembered, first, that their material was collected chiefly from the various goitrous regions and, second, that true benign tumors were apparently included in the same category as nodose goiter. All observers agree, however, that a constant increase in the incidence of nodules is seen with advancing age.

STUDY OF NODULES

A pathologic analysis of the 41 specimens of nodular goiter macroscopically revealed that 17, or 40.1 per cent, contained a single nodule and that 24, or 59.9 per cent, had multiple tumefactions. None of the specimens contained more than six nodules. The nodules varied from approximately 0.5 to 5 cm. in diameter. Most of them were firm, yellow or grayish white, localized and encapsulated colloid-bearing areas surrounded by thin or dense gray-white connective tissue. The cut surface was either smooth or granular. A few contained a brown hemorrhagic substance. Others appeared scarred and cystic.

Histologically, the nodular element was composed as follows: Eighteen, or 43.1 per cent, of the nodules presented circumscribed and apparently encapsulated areas consisting of small acini which varied from small round follicles to clusters of three, four and five cells, practically devoid of colloid and peripherally situated. The larger and colloid-containing acini were more centrally located. All of these tumefactions showed evidence of residual hypertrophy and hyperplasia, and in many instances hemorrhage, necrosis, scarring, hyalinization and other sequelae of extreme involution existed. In the majority of cases either the fetal or the colloid type of follicle predominated, so that the growths closely resembled mixed fetal and colloid adenomas.

Eleven, or 26.9 per cent, of these tumors were colloid cysts. These appeared as large, scattered, round epithelium-lined structures, varying in size and number and containing an abundance of evenly stained colloid. What was apparently the capsule consisted both of fibrous connective tissue and of compressed normal thyroid follicles. Focal hypertrophy and hyperplasia and a moderate amount of degenerative change were present.

Five, or 12.9 per cent, of the nodules consisted of thyroid follicles of the fetal type, without colloid and closely resembling so-called fetal adenomas. Four, or 9.8 per cent, were circumscribed areas composed

of numerous large, dilated acini lined with flattened epithelium and filled with colloid. In these the capsule consisted of connective tissue or compressed thyroid parenchyma or both, together with evidence of previous hypertrophy and hyperplasia and moderate degenerative changes. Microscopically these tumors were indistinguishable from so-called colloid adenomas.

The remainder of the nodules (3, or 7.3 per cent) consisted of areas made up of small round follicles with tiny lumens and with localized areas of lymphocytic infiltration in the surrounding stroma. Although the epithelium in these areas was hyperplastic, it did not parallel the amount of involutional change noted in the follicular epithelium surrounding them. This fact gave me the impression that these regions had made an abortive attempt to complete the process of involution. Histologically these islands were similar to those described by Ewing [10] and other observers as "miliary or diffuse adenomata." MacCallum [11] suggested that "these were areas in which the disease process was beginning all over again." Occasionally, in these tumefactions small mounds of enfolded hyperplastic epithelium were encountered, superimposed on epithelium which had apparently undergone hypertrophy and hyperplasia. This process I termed "adenomatoid hyperplasia," and it appeared to be indicative of secondary hypertrophy and hyperplasia concomitant with a previous exacerbation. In the many instances in which the histologic evidence showed that hypertrophy and hyperplasia had occurred outside as well as inside the nodule, it was some proof that this process had probably been a diffuse one which had involved the gland as a whole instead of being localized and confined to certain specific regions of the organ. Rienhoff, in his study of 109 cases of nodular goiter associated with hyperthyroidism, found this to be true in 34 per cent of cases, the morbid process being localized in 58 per cent. In 1905, MacCallum, in describing the histologic changes associated with hypertrophy and hyperplasia in cases of exophthalmic goiter, stated that this morbid process might be confined "to small patches here and there throughout a gland which otherwise seems normal. Microscopically, the altered areas are quite sharply demarcated from the rest and may involve a great number of alveoli or be limited to very small foci, including only a few alveoli here and there."

10. Ewing, J.: An Histological Study of the Thyroid, Tr. A. Am. Physicians **21**:567, 1906.

11. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158 (Oct. 5) 1907.

It is apparent from the pathologic data on the material so far analyzed that practically every type of involutional irregularity was encountered, ranging from the changes associated with hypoinvolution to degenerative sequelae of extreme regression. This would seem to substantiate the conclusion of Rienhoff, namely, that these tumefactions are not true pathologic entities but are simply the result of the inactive phase of the disease cycle, whether spontaneous or artificial, following a previous overactivity of the thyroid parenchyma. In the pathologic analysis of his cases of nodular goiter, Rice, in 1931, found colloid nodules to be prevalent, occurring in 83.3 per cent of the glands. The parenchymatous nodules, or those resembling so-called fetal adenomas, were present in 25.2 per cent of his cases, and intermediate nodules were present in 8.1 per cent. The latter have the characteristics both of fetal and of colloid adenomas. Degenerative changes were observed in 12.4 per cent of the nodose goiters examined by Rice.

TRUE BENIGN TUMOR

Histologic examination of the specimens considered as representative of true benign tumors showed them to present a fairly characteristic picture of their neoplastic nature. In this group were included 25 simple adenomas and 9 fetal adenomas. Although the latter group showed many of the microscopic features distinctive of fetal adenoma, sections from various portions of the glands containing simple adenomas in some instances presented a heterogeneous picture. While the majority of the circumscribed masses suggested cellular proliferation and regeneration as well, with the typical histologic changes denoting hypertrophy and hyperplasia of the surrounding parenchyma, a few presented evidence of histologic regression, indicating that involution had occurred. In some cases, therefore, it was difficult to draw a sharp line between tumefactions resulting from hyperplasia and involution on the one hand and true tumor growths on the other. MacCallum stated that "the thyroid adenomata are extremely common and here again it is sometimes difficult to feel sure that we are dealing with actual tumors and not with hyperplasia of the functioning gland." Rienhoff, in his series of 109 cases of nodular goiter associated with hyperthyroidism, reported that 8 per cent of the nodules were true benign adenomas.

There is no doubt that the term adenoma as encountered in the literature on the thyroid gland has served as an expression of some of the bizarre histologic interpretations of various investigators. The pathogenesis of this tumor, particularly of fetal adenoma, has also been a point of controversy for many years. Wölfler, cited by Rienhoff,[12] in 1883 introduced the conception of its origin from a fetal

12. Rienhoff, F. W.: A New Conception of Some Morbid Changes in Diseases of the Thyroid Gland, West. J. Surg. **39**:421, 1931.

rest. Wilson, in 1913, characterized "adenomatosis" by diffuse new formation of acini usually involving the entire thyroid gland, beginning with the fetal type without secretion and proceeding to the adult, or colloid, type. Goetsch,[14] in 1920 and in 1921, described "diffuse adenomatosis" as the early stage of adenoma and considered the formation of new acini "an abortive attempt at the formation of young, small alveoli."

Else,[15] in 1925, in studying the pathogenesis of adenomatosis, which he regarded as a pathologic entity, concluded that the fetal type of acinus arises from masses of undifferentiated cells which are probably identical with those described by Wölfler as interstitial cells. This fetal acinus subsequently develops into a more adult type of colloid follicle. He further stated that "taking the picture as a whole, it gives one the impression of a diffuse new acinous formation in which certain areas have developed more rapidly than others, thus producing the nodular effect."

Hertzler,[16] in 1928, spoke of bosselations and of the development of acini from masses of cells without lumens in the interstitial spaces. Marine and Lenhartz,[17] in 1911, regarded simple and fetal adenomas as benign tumors possessing many attributes of ordinary hyperplasia and some features common to tumors. They explained that "the fetal adenomas have a period of active growth followed by a period of cessation of growth, and finally pass into a colloid or resting state." Fetal adenomas were not affected by iodine, and simple adenomas were only slightly so, in comparison with the ordinary hyperplasias.

Boyd[18] considered nodules of the fetal type as only varieties of colloid adenoma. Murphy and Ahnquist,[19] in 1937, described "fetal pattern," that is, the arrangement of the acinus, and not the acinus itself, as the distinctive feature of fetal adenomas and stated that the appearance of these nodules is really due to the cellular proliferation occurring in a colloid acinus, apparently supporting the growth and thereby eliminating the necessity of fibrous supporting tissue.

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13. Footnote deleted on proof.

14. Goetsch, E.: Disorders of the Thyroid Gland, Endocrinology **4**:387, 1920.

15. Else, J. E.: Adenomatosis, or the Diffuse Adenomatous Goiter, J. A. M. A. **85**:1878 (Dec. 12) 1925.

16. Hertzler, A. E.: Mixed Tumors of the Thyroid Gland, Arch. Surg. **16**:1187 (June) 1928.

17. Marine, D., and Lenhartz, C. H.: The Pathological Anatomy of the Human Thyroid Gland, Arch. Int. Med. **7**:506 (April) 1911.

18. Boyd, W.: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1933.

19. Murphy, W. B., and Ahnquist, G.: Origin of Fetal Adenoma in the Thyroid Gland, Arch. Surg. **35**:211 (Aug.) 1937.

RELATION OF TRUE BENIGN ADENOMA TO HYPERTHYROIDISM

In view of the references to "toxic adenoma" constantly appearing in the literature,[20] a clinical analysis of the 34 cases of true benign neoplasm was made for the purpose of determining whether the tumors were responsible for the clinical manifestations associated with hyperthyroidism. The clinical records of the patients were consulted, and data on the following points were tabulated for each case:

1. Clinical signs and symptoms of hyperthyroidism.
2. Clinical condition of the thyroid gland.
3. Preoperative and postoperative basal metabolic rates.
4. Type of operative procedure.
5. Preoperative and postoperative diagnosis.

Many of the symptoms of hyperthyroidism, such as nervousness, palpitation, loss of weight and tachycardia, were not considered significant in this study, as they are variable factors and are likely to be encountered in conditions other than hyperthyroidism or exophthalmic goiter. Because of this only the objective findings were deemed of any importance.

Clinical analysis revealed glandular enlargement of different degrees in all of these cases. In the majority the mass was symmetric and soft. In a few it was either hard and nodular or soft and nodular. A little more than half of the patients had either visible pulsations of the neck or a systolic bruit at the upper poles. Exophthalmos of varying severity occurred in 15, or 44 per cent; 28, or 82 per cent, had tremors of the lids, tongue or upper extremities. The preoperative basal metabolic rates varied from — 10 per cent to + 88 per cent. The average rate was + 32.6 per cent. (The patient whose basal metabolic rate was — 10 per cent was a boy 15 years of age who had been treated in the clinic for cretinism for the preceding ten years and in

20. (*a*) Clute, H. M., and Smith, L. W.: Cancer of the Thyroid Gland, Arch. Surg. **18**:1 (Jan.) 1929. (*b*) Williamson, W. G., and Pearse, I. H.: The Pathological Classification of Goiter, J. Path. & Bact. **28**:361, 1925. (*c*) Kline, B. S.: The Origin of Adenomatous Goiter, Am. J. Path. **1**:235, 1925. (*d*) Marine, D: Special Cytology, New York, Paul B. Hoeber, Inc., 1932. (*e*) Rienhoff, F. W.: The Histological Changes Brought About in Cases of Exophthalmic Goiter, Bull. Johns Hopkins Hosp. **37**:285, 1925. (*f*) Thomas, H. M., Jr.: Nodular Goiter with Hyperthyroidism, Arch. Surg. **16**:117 (Jan., pt. 1) 1928. (*g*) Plummer, H. S.: The Clinical and Pathological Relationship of Simple and Exophthalmic Goiter, Am. J. M. Sc. **146**:790, 1913. (*h*) Horsley, V.: Browne Lecture, Lancet **2**:1163, 1886. (*i*) Biedl, A.: Thyroid and Hypophyseal Pathology, Ann. Clin. Med. **3**:444, 1924. (*j*) Halsted, W. S.: An Experimental Study of the Thyroid Gland of Dogs, with Especial Consideration of Hypertrophy of This Gland, Johns Hopkins Hosp. Rep. **1**:373, 1896.

whom a swelling of the neck had developed during the four years immediately preceding this study. The mass was removed because of its mechanical pressure effect.) The average postoperative basal metabolic rate was + 8.6 per cent.

The fact that partial lobectomies were performed on all of these patients and were followed in all cases by clinical improvement of the condition and by a fall of the basal metabolic rate would lend some support to the hypothesis that these tumors can become toxic. This, however, is not conclusive proof that the growths and not the concomitant overactivity of the remaining thyroid parenchyma are responsible for the clinical manifestations of hyperthyroidism.

INCIDENCE OF CARCINOMA

In this series of 216 cases, primary carcinoma comprised 5.6 per cent of all true tumors, representing an incidence of 0.93 per cent of the total number of thyroids. Clute and Smith,[20a] in a study of 3,389 cases of disturbance of the thyroid gland, found carcinoma in 67 patients, an incidence of 1.68 per cent. They reported that "an adenomatous goiter preceded the malignant disease in 94.4 per cent of the cases studied." In their group of cases the youngest patient with carcinoma was a woman aged 20 and the oldest a woman aged 82.

Clute and Smith [20a] stated:

> Portmann, in Cleveland, reported an incidence of 1.6 percent of malignant disease in persons with thyroid disturbance. Graham found less than 2 percent of malignant disease in thyroids examined at Lakeside Hospital. Eberts and Fitzgerald gave an incidence of 1.8 percent in 612 operative cases of thyroid disease. Craven found carcinoma in 1 to 5 percent of all the thyroids he operated on.

SUMMARY AND CONCLUSIONS

Of the 216 surgically removed thyroids studied, diffuse hyperplasia occurred in 64.3 per cent, while nodular goiter and the true tumors, occurring with almost equal frequency, occurred in 19 per cent and 16.7 per cent respectively.

The frequency of nodular goiter is increased with advancing age, particularly in women.

While there were six times as many women as men with nodular goiter, true tumors of the thyroid gland occurred only twice as often in women.

Practically every one of these pathologic states of the thyroid gland occurred, roughly, one and one-half times as frequently in parous as in nulliparous women, but for simple benign adenoma the converse was true.

The nodules encountered in most cases of nodular goiter are not true pathologic entities but simply involutional bodies, the result of the involutional cycle of hyperplasia.

Many of these involutional bodies are histologically indistinguishable from true benign adenoma.

While malignant disease of the thyroid gland constituted 5.6 per cent of all the true tumors, the incidence of carcinoma was only 0.93 per cent for the entire group of 216 cases.

There is as yet no conclusive proof that the clinical manifestations of hyperthyroidism are due solely to hyperactivity of so-called true benign adenoma and not to the hypertrophy and hyperplasia occurring simultaneously with the tumor.

ASEPTIC NECROSIS OF THE FEMORAL HEAD FOLLOWING TRAUMATIC DISLOCATION

REPORT OF TWO CASES

SAMUEL KLEINBERG, M.D.
NEW YORK

Increasing experience with various histopathologic disturbances of bones and joints has emphasized the frequent occurrence of aseptic necrosis of the head of the femur in fracture and fracture-dislocation at the hip, Legg-Perthes disease, certain congenital dislocations of the hip, and, more recently simple traumatic dislocations of the hip. The pathologic process in all of these conditions seems identical, being due apparently to interference with or interruption of the vascular supply through the ligamentum teres. Aseptic necrosis of the femoral head after simple dislocation is attracting special attention because in the majority of cases when the lesion is recognized irreparable damage has already occurred and the function of the hip has been permanently compromised. Yet it would appear that if the potential injury to the femoral head after a dislocation were appreciated and anticipated the treatment might be so ordered that it would prevent much of the damage to the femoral head and would preserve the motion of the hip joint.

A knowledge of the vascular supply of the head and neck of the femur is necessary for an understanding of the pathogenesis and pathologic picture of aseptic necrosis in this region. There used to be considerable difference of opinion in regard to the exact sources of the blood supply to the femoral head. This applied particularly to the part played by the ligamentum teres. It was contended by some that the vessels are patent in infancy and childhood but that all or many of them become obliterated during adolescence and that all are entirely closed during adult life. Recent studies of the blood supply of the ligamentum teres have provided interesting observations. Kolodny,[1] in an investigation of the angiologic structure of the head and neck of the femur, concluded: "These results of our study lead us to the conclusion that the blood vessels brought to the head of the femur in the ligamentum teres play a certain role in the nutrition of the femoral head in the new born and children, but are of no perceptible importance in the nutrition of

1. Kolodny, A.: The Architecture and the Blood Supply of the Head and Neck of the Femur and Their Importance in the Pathology of Fractures of the Neck, J. Bone & Joint Surg. **7**:575-597 (July) 1925.

the femoral head of the adult." On the other hand, Chandler and Kreuscher,[2] after an anatomic study of 114 round ligaments from 68 adult cadavers varying in age at death from 25 to 75 years, stated: "All ligaments contained vessels. In four cases the vessels were of precapillary size. All other ligaments contained a significant blood supply." "Serial sections of the junction of the ligament with the femur demonstrate an anastomosis between the vessels in the ligament and those of the head of the femur." Wolcott,[3] studying the blood supply of the femoral head, had occasion to examine the round ligaments in 4 old persons on whom reconstruction operations had been performed for ununited fractures at the hip. These patients varied in age from 60 to 75 years. In each case the ligamentum teres had unmistakably patent blood vessels. Zemansky and Lippman,[4] experimenting on rabbits, concluded that "the vessels of the round ligament are essential, at least in rabbits, for the normal development of the femoral head."

In a study which is currently being conducted in my service at the Hospital for Joint Diseases my associates and I have under observation 5 patients, varying in age between 5 and 15 years, in whom there is unquestionable evidence of the presence of patent arteries and veins in the round ligaments. I have a specimen, a femoral head removed during a Whitman reconstruction operation for ununited fracture of the neck of the femur in a woman 55 years of age, in which a vertical section shows that in the proximal part of the head, over a segment of about ¾ inch (1.9 cm.) subjacent and adjacent to the fovea capitis, the bone is reddish (the rest being gray), indicating definitely that the vessels from the ligamentum teres supplied blood to and kept alive this part of the head.

Thus, the head of the femur gets its blood supply from three sources: (1) the interior of the neck, (2) the capsular vessels and (3) the ligamentum teres. The vessels from the ligamentum teres are distributed to a variable segment of the head in the immediate vicinity of the fovea. The capsular vessels supply the periphery and a large part of the head. The blood vessels from the interior of the neck nourish the epiphysial plate. All observers agree that these three sources

2. Chandler, S. B., and Kreuscher, P. H.: A Study of the Blood Supply to the Ligamentum Teres and Its Relation to the Circulation of the Head of the Femur, J. Bone & Joint Surg. **14**:835-846 (Oct.) 1932.

3. Wolcott, W. E.: Circulation of the Head and Neck of the Femur: Its Relation to Non-Union in Fractures of the Femoral Neck, J. A. M. A. **100**: 27-34 (Jan. 7) 1933.

4. Zemansky, A. P., Jr., and Lippman, R. K.: The Importance of the Vessels in the Round Ligament to the Head of the Femur During the Period of Growth, and Their Possible Relationship to Perthes' Disease, Surg., Gynec. & Obst. **48**: 461-469 (April) 1929.

are always present in infancy and childhood. There is doubt in the minds of some whether the vessels in the ligamentum teres remain open in adult life, although there is indubitable evidence from both anatomic and clinical studies that these vessels, at least in some persons, persist even to old age. In most parts of the body there is liberal anastomosis of the vessels entering a given area. This is not true of the femoral head, in which many of the blood vessels are of the terminal type, so that there is poor vascular anastomosis. Interference with or interruption of the blood supply to the top of the head through the ligamentum teres therefore is likely to be followed by aseptic necrosis of the bone and cartilage in the involved area. The extent of the original necrosis in the event of damage to the ligamentum teres is manifestly dependent on the collateral circulation available from the capsular arteries. Chandler [5] stated: "Those areas which are less liberally supplied with vascular anastomoses necessarily have lower factors of safety and become more vulnerable to the effects of vascular interruption." The literature now contains reports of cases in which trauma caused injury to the ligamentum teres with consequent necrosis of the top of the femoral head, the patients including both children and adults. Phemister [6] reported 4 such cases. Chandler and Kreuscher [2] reported 1 case of aseptic necrosis of the femoral head following a fracture of the acetabulum and central dislocation of the femoral head. At the last meeting of the American Orthopaedic Association, Potts, of Buffalo, reported 5 cases of aseptic necrosis of the head of the femur, the lesion in each instance following a traumatic dislocation. I wish to record 2 cases in which aseptic necrosis followed traumatic dislocation of the hip, the patients being young adults.

Buchman and I [7] have found in operating on patients for chronic marked slipping of the femoral capital epiphysis that if after operative realinement and pegging of the head and neck of the femur we prevent direct weight bearing on the femoral head for one year and in some cases even longer (up to two years) the femoral head gradually becomes revascularized and reformed by the process of creeping substitution so well described by Phemister. In the cases of aseptic necrosis of the femoral head following dislocation so far reported there resulted great deformity of the head and disturbance of articular function, even to ankylosis. In every one of these cases, however, weight bearing was

5. Chandler, F. A.: Aseptic Necrosis of the Head of the Femur, Wisconsin M. J. **35**:609 (Aug.) 1936.

6. Phemister, D. B.: Fractures of Neck of Femur, Dislocations of the Hip, and Obscure Vascular Disturbances Producing Aseptic Necrosis of Head of Femur, Surg., Gynec. & Obst. **59**:414-440 (Sept.) 1934.

7. Kleinberg, S., and Buchman, J.: The Operative Versus the Manipulative Treatment of Slipped Femoral Epiphysis, with a Description of a Curative Operation, J. A. M. A. **107**:1545-1551 (Nov. 7) 1936.

permitted within an average of three months after the injury, which is, I believe, much too early. In other words, not only was there an interruption of the blood supply to the top of the femoral head, with consequent necrosis of the summit of the head, but weight bearing hastened the collapse of the affected bone.

From a review of the cases of aseptic necrosis of the femoral head following traumatic dislocation reported in the literature and from my own experience, the various aspects of the illness may be summarized in the following manner.

CLINICAL HISTORY AND COURSE OF THE ILLNESS

The original injury is a traumatic dislocation. After the reduction, which in some instances is difficult and may entail considerable forcible manipulation, the roentgenogram shows a satisfactory replacement of the femoral head, which appears normal in structure and outline. There is naturally some pain and disability, and for several weeks the patient remains in bed. As the discomfort subsides, walking is begun, at first with the aid of crutches or a cane and soon without any external support. Walking becomes increasingly easier, and the patient, usually a young adult, becomes active and may even engage in various sports. After several months there reappear some discomfort in the limb and stiffness at the hip. At the beginning these symptoms are present only when the patient begins to walk. There is difficulty in getting into and out of a chair. Soon the patient finds that he cannot run or walk as well, as far or as fast as he used to. The stiffness and pain increase and become constant.

Physical examination reveals a limp. The hip is moderately flexed and adducted, and all motions are restricted to variable degrees. Forced motion, as on manipulation, is painful. There is little or no local tenderness and no shortening.

The roentgen picture shows a lesion in the proximal segment or summit of the femoral head. In the early stages one sees a distinct line of demarcation between the pathologic and the normal bone. This corresponds roughly to the region directly above the epiphysial plate. In the summit of the femoral head the articular surface is irregular and the texture of the bone is altered; it is very dense, with some spots of rarefaction. In the later stages there may be some loose fragments of bone and, not infrequently, osteophytes projecting from the periphery of the head of the femur. This bony hypertrophy is the result of the effort at repair contributed by the capsular vessels. Ultimately there is extensive arthritis, with partial or complete ankylosis.

Gross Pathologic Picture.—On exposing the hip joint one finds congestion and thickening of the capsule with hypertrophy of the synovial lining. There may be some loose fragments and spicules of bone

about the head at its junction with the neck. The top of the femoral head is uneven. The cartilage may be raised from the underlying bone (so-called blistering). Parts of the cartilage may be eroded or entirely loose. There may be cracks in the cartilage. The subchondral bone appears bloodless. If a drill is inserted into the head no blood is obtained until the drill perforates the bone distal to the epiphysial plate.

Microscopic Pathologic Picture.—The synovia is thickened and congested and may show collections of lymphocytes. The subchondral bone shows necrosis but no inflammatory tissue; that is, there is aseptic necrosis with collapse of the bony trabeculae. There is hyaline degeneration of the articular cartilage. The histopathologic picture is much like that of Legg-Perthes disease.

In all of the cases thus far reported, early weight bearing was permitted. It is not possible to state what the ultimate changes would have been had the femoral head not been permitted to bear weight. However, from my experience in the treatment of chronic slipping of the femoral capital epiphysis (I do not permit direct weight bearing for a year or longer) I believe that if after reduction of a traumatic dislocation in a young person weight bearing were prohibited, the collateral circulation from the capsular vessels and the vessels of the femoral neck would in time revascularize the damaged section of the head, which ultimately through creeping substitution would be replaced by normal bone.

REPORT OF CASES

CASE 1.—Thomas C., 16 years old, was admitted to my service at the Hospital for Joint Diseases on March 20, 1938. His chief complaints were pain and stiffness in the right hip. He had fallen from a milk truck on Feb. 11, 1937, sustaining a dislocation of the right hip. The dislocation was reduced, and a plaster of paris spica was applied. This was removed at the end of three weeks, and the patient was allowed to walk, using a cane, which was discarded two weeks later. He rapidly increased his activity and shortly was playing basketball. In October, eight months after the injury, the hip became painful and he began to limp. Soon thereafter it was noted that the affected limb was shorter than the opposite limb.

Examination on admission showed the patient to be in good general condition, walking with a marked limp on the right side. The right lower limb was in an attitude of flexion, adduction and outward rotation at the hip. The angle of greatest extension at the hip was 145 degrees, that of flexion, 110 degrees. There were a few degrees of rotation and no abduction or adduction. There was no local tenderness at the hip, but there was 1 inch (3.1 cm.) atrophy of the thigh.

Roentgen Examination.—The original roentgenogram (fig. 1 *A*), dated Feb. 12, 1937, showed a dorsal dislocation of the hip. After the reduction, a roentgenogram (fig. 1 *B*) showed that the femoral head was normal in shape, size and structure. There was no evidence of damage, such as fracture, to the head itself. The film (fig. 2) made on March 20, 1938, thirteen months after the injury, showed an extensive lesion of the femoral head. The top of the head, above the epiphysial line, appeared as a dense crescentic mass with some normal-looking bone at each extremity. Underneath this dense bone was a ragged line of rarefied tissue, pre-

sumably the epiphysial cartilage, below which was a border of sclerotic bone. The neck at the upper extremity of its outer border projected upward beyond the head as a large conical spicule. The acetabulum showed no gross abnormality. The top of the femoral head appeared like a sequestrum.

Operation.—An operation was decided on for the purpose of drilling through the femoral head and neck in the hope of revascularizing the sclerotic head. The hip was exposed through an anterior Smith-Petersen incision. When the capsule was cut through there was a gush of fluid; this proved on culture to be sterile. When the capsule was retracted there came into view three strips of articular cartilage 1 by ¼ inch (2.5 by 0.6 cm.), attached to one another and to the outer surface of the femoral head but loose and raised from the bone in their centers. The femoral head was enlarged; the fovea could not be identified. On the anterior surface of the neck was a flat osteochondral mass entirely free except at its base, where it was attached to the neck. This was removed. The neck was everywhere covered by synovial tissue, which in places was ½ inch (1.3 cm.) thick and

Fig. 1.—*A,* roentgenogram taken Feb. 12, 1937, before reduction, showing the femoral head out of and above the acetabulum. *B,* roentgenogram taken February 13, directly after the reduction. Note the replacement of the femoral head in the acetabulum. There is no evidence of injury to or deformity of any part of the head of the femur.

markedly congested. The inner surface of the capsule was entirely covered with thick, beefy synovial tissue. The head of the femur was then dislocated from the acetabulum. There was no ligamentum teres. Around the upper two fifths of the head was a circular linear depression. Within this area the articular cartilage was rough in some spots, eroded in others and entirely loose in several places. At the line of depression the cartilage was thin, and there were two loose tabs of cartilage, one on the anterior and the other on the posterior surface of the head. Twelve drill holes were made through the disorganized cartilage on the summit of the head. These penetrated the neck. The subchondral bone was abnormally soft in some areas and very hard in others. After each drill hole was made some moments passed before blood appeared. Evidently, the subchondral bone was anemic and the blood welled up from the deeper bone in the femoral neck. The acetabulum on inspection and palpation seemed normal. The femoral head was

replaced in the acetabulum, the wound was closed without drainage, and a plaster spica was applied.

The gross pathologic observations consisted of (1) an enlarged femoral head, (2) absence of the fovea capitis, (3) absence of the ligamentum teres, (4) a circular depression on the top of the head, including within its confines about two fifths of the head, (5) irregularity and looseness of the articular cartilage, (6) numerous cartilaginous tabs, (7) extensive synovitis and (8) two osteochondral bodies projecting from the femoral neck.

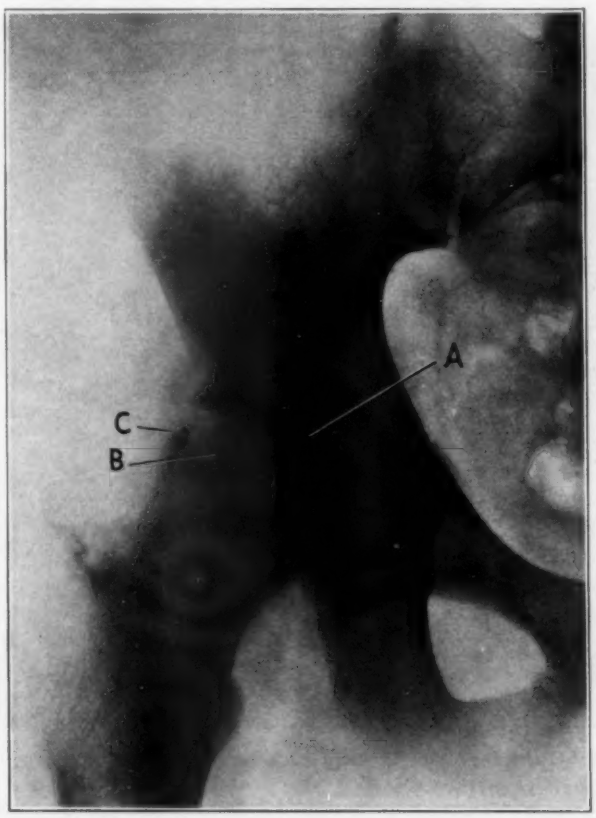

Fig. 2.—Roentgenogram taken March 20, 1938. There is deformity of the femoral head. The summit of the head is sclerotic and is the site of aseptic necrosis (*A*). At *B* are seen the remains of the epiphysial plate. Note (*C*) an osteophyte; this represents an effort at repair on the part of the capsular blood vessels supplying the periphery of the head.

The patient is still under observation, walking with a Thomas caliper brace and an ischial crutch and receiving physical therapy for mobilization of the hip joint. It is too soon to be certain of the ultimate result of this late operative intervention.

The various specimens removed from the hip joint (fig. 3) showed (1) villous hypertrophy of the synovial membrane, which contained in places collections of lymphocytes, (2) degenerated articular cartilage and (3) necrotic bone.

Summary of Case.—I believe that in this instance the pathologic condition in the hip was a sequel to a tear of the ligamentum teres during the original dislocation. The blood supply to the top of the head was thereby cut off, and the subchondral bone and articular cartilage died from inanition. The top of the head became a loose body. There resulted a reactionary inflammation in the capsule and synovial tissue. The damage to the femoral head from its loss of blood supply was increased by weight bearing, which crushed the bone and accelerated the degeneration of the tissue before an adequate collateral blood supply could be established.

Fig. 3.—Photomicrograph showing necrosis of bone: (*A*) fragmenting and necrosing bone; (*B*) detritus, and (*C*) dead bone.

Case 2.—Herbert S., 20 years old, consulted me on June 3, 1938 for stiffness in the right hip and pain in the right hip and knee. He had dislocated his right hip in September 1937 in an automobile accident. The dislocation was reduced, with the patient under the influence of an anesthetic, and a plaster of paris support was applied. This was removed after four weeks, and physical therapy was instituted. He improved at first very rapidly; during February and March he had free motion in the hip and was engaging vigorously in athletics. Since then pain and stiffness have set in, so that at the time of writing he has less motion in the hip than in March. In particular, he has difficulty in getting into and out of a chair.

Examination showed him to be in excellent general condition. He walked with a limp on the right side. Extension of the hip was normal, while flexion was checked at 80 degrees. Abduction was limited to 5 degrees and adduction to 20

degrees. Rotation was restricted to a fourth of the normal range. The limbs were of equal length.

Roentgen Examination.—A roentgenogram made in October 1937, several weeks after the dislocation was reduced, showed not only that the head of the femur was in the acetabulum but that the head appeared normal in contour and structure. There was a shadow, as of a sliver of bone lying along the lateral margin of the head and neck, extending down to about ½ inch (1.2 cm.) of the greater trochanter. There was no defect anywhere to indicate the origin of this fragment of bone. A roentgenogram made on November 26 showed that the articular cartilage of the femoral head was smooth. The para-articular shadow had almost completely disappeared. A lateral view showed a little rarefaction and an oblique indentation in the outer surface of the head at its junction with the neck. Roentgenograms made in April 1938 exhibited a marked alteration in the architecture of the femoral head. There was sclerosis of the top of the head with irregular rarefaction at the epiphysial line. The joint was hazy. One film showed a line of rarefaction extending from the articular surface, a little to the inner side of the fovea, obliquely downward and outward to the junction of the head and neck. There was a bony spicule formation at the junction of the head and neck on the outer side, at the extremity of the oblique line of rarefaction or depression. The previously noted para-articular shadow was represented by two small pieces of bone. The articular cartilage of the head was hazy and irregular. There was rarefaction of the juxta-epiphysial bone in the neck. Roentgenograms made on May 19, eight months after the injury, showed irregularity of the articular cartilage of the femoral head, rarefaction of the neck of the femur, some loose fragments of bone and marked sclerosis of the upper segment of the head.

Summary of Case.—In this, as in the previous case, not only was the circulation of the head disturbed by a tear of the ligamentum teres during the dislocation, but the resumption of weight bearing four weeks later further traumatized the femoral head, causing disorganization of its upper segment. The final result was necrosis of the top of the head and severe disturbance of the function of the hip joint. There was one factor in this case which was not present in case 1, namely, the presence of a shadow of ossific density in the lateral portion of the hip. Whether this represented calcification and ossification of a portion of the capsule that was injured or an actual fracture of a part of the head cannot be decided except by opening the joint. Otherwise the history, course and roentgen changes are similar to those noted in the first case.

TREATMENT

The treatment given my patients after the reduction of the dislocation may have appeared logical in that function was resumed when the irritative symptoms following the injury subsided, but in the light of the ultimate poor function it was not satisfactory. I have indicated why early weight bearing has a harmful effect. The ability of the patient to resume walking within a few weeks after so severe an injury as a traumatic dislocation of the hip may be gratifying to the surgeon and the parents, but with an eye to the ultimate service of the hip it is imperative that weight bearing be interdicted until it is safe. While I have no cases of aseptic necrosis of the femoral head to prove the truth of my suggestion, I may refer to the value of walking without weight bearing

in cases of Legg-Perthes disease and epiphysial slipping, in which the histopathologic appearance of the bone is similar.

I suggest, therefore, that in a case of traumatic dislocation of the hip the reduction should be effected by the gentlest measure that will return the femoral head into the acetabulum. If great manipulative force is necessary it may be better to reduce the dislocation by open operation, in which only gentle handling would serve to replace the head. In this detail there is a precedent in the treatment of congenital dislocations of the hip, for which one now never uses great force. After the reduction and immobilization one should keep the patient in bed for several weeks to allow the irritation incidental to the trauma of the dislocation to subside. One should then apply a Thomas caliper brace. The brace should be somewhat too long in order to assure lack of weight bearing through the hip. Furthermore, a well fitting ischial ring should be attached, so that all of the weight on the affected side may be transmitted through the ischium. This brace should be worn for a year or even longer, until there is complete reformation of the femoral head in outline and especially in texture. The brace must not be removed until the substance of the femoral head has the quality of the adjacent bone. In the meantime, physical therapy (baking, massage, hydrotherapy and active and passive exercises) may be utilized to aid return of normal function.

SUMMARY

Two cases are reported in which in a young adult after a traumatic dislocation of the hip the top of the femoral head underwent aseptic necrosis. This lesion resulted from interruption of the blood supply through the ligamentum teres, which was ruptured during the dislocation. The necrotic process was exaggerated by too early weight bearing, which caused crushing of the devitalized bone. Secondary synovitis set in, with increase in the synovial fluid and formation of a pannus on the neck of the femur. Some osteophytes appeared on the femoral head at its junction with the neck, representing undoubtedly an attempt at repair. The articular cartilage was seriously damaged; macroscopically it was found to be eroded, elevated from the underlying bone and even reduced to tabs or shreds; microscopically it showed extensive hyaline degeneration. The pathologic process resulted in what appeared clinically as arthritis with flexion and adduction deformity of the hip and severe limitation of its function. The experience in my cases and in those reported by other observers leads me to the conclusion that less damage would be incurred and an opportunity for better anatomic and functional result would be provided if in this type of injury no weight bearing were allowed until complete healing, as evidenced roentgenographically by normal bony structure in the femoral head, has occurred.

TUMORS OF THE SMALL INTESTINE

SIDNEY COHN, M.D.

JOSEPH A. LANDY, M.D.
AND
MAX RICHTER, M.D.
NEW YORK

Tumors of the small intestine are not medical curiosities, yet it is rare to find more than a paragraph or two devoted to this subject in the average textbook on surgery. A search through the literature reveals that hundreds of cases have been reported, and it is a small hospital that does not have several examples among its records. What, then, is the reason for this relative obscurity? In the first place, tumors of other parts of the gastrointestinal tract occur more frequently; hence they are deserving of primary recognition. Secondly, the diagnosis of tumor of the small intestine is made with difficulty; as a matter of fact, the disease is often first recognized during an operation performed for the relief of a complication. The purpose of this paper will be well served if it results in a proper evaluation of the clinical importance of this group of diseases.

In 1919, Judd [1] stated that a number of clinics had reported finding 3 per cent of intestinal carcinomas in the small bowel, although the 24 cases which he described formed a much smaller incidence. Ewing [2] also estimated the frequency of malignant tumors of the small intestine at 3 per cent of all found in the gastrointestinal tract. Rankin and Mayo [3] reported that up to 1929 there were 55 cases of carcinoma of the small intestine at the Mayo Clinic, as compared with 4,597 cases of carcinoma of the large intestine and rectum and 4,335 cases of carcinoma of the stomach. Raiford,[4] in his excellent review of the

From the surgical service of Dr. Cohn and from the private practice of Dr. Cohn and Dr. Landy at the Bronx Hospital.

1. Judd, E. S.: Carcinoma of the Small Intestine, Journal-Lancet **39**:159, 1919.

2. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928.

3. Rankin, F. W., and Mayo, C.: Carcinoma of the Small Bowel, Surg., Gynec. & Obst. **50**:939, 1930.

4. Raiford, T. S.: Tumors of the Small Intestine, Arch. Surg. **25**:122 (July) 1932.

subject, pointed out that in a series of 986 tumors of the intestinal tract at the Johns Hopkins Hospital, 88 tumors, or 8.9 per cent, were in the small bowel. In his series there were 776 malignant tumors, of which 38, or 4.9 per cent, were situated in the small intestine. There were 210 benign tumors, of which 50, or 23.8 per cent, were located in the small bowel. These figures show that both types of tumor are more frequent in the large intestine and in the stomach, but in the small intestine tumors are predominantly benign, while in other parts of the gastrointestinal tract they are predominantly malignant.

MALIGNANT TUMORS

Carcinoma.—Carcinoma is one of the most frequently encountered malignant tumors of the small intestine. In most reported series it is found in approximately 3 per cent of the total number of carcinomas of the gastrointestinal tract. In the Mayo Clinic series the average age of the patients was 47.5 years. The growth occurs twice as often in males as in females.

Most observers agree that the duodenum is the most frequent site of carcinoma of the small bowel. In Raiford's series 8 of 16 tumors were in the duodenum. Rankin and Mayo, however, stated that 21 of the 55 tumors described by them were in the jejunum. Considering the relative shortness of the duodenum, the frequent finding of carcinoma there is noteworthy. If the duodenum is divided into three parts, namely, preampullary, periampullary and prejejunal, the periampullary region is undoubtedly the most frequent site of carcinoma. This explains the frequency of involvement of the ampulla of Vater.

The most usual types of carcinoma of the small intestine are adenocarcinoma and medullary carcinoma. The growths are most often on the annular or constricting form, but polypoid and ulcerative infiltrating growths are also seen. Adenocarcinoma is easily recognized microscopically by its atypical glandular formation and infiltrating malignant cells. Medullary carcinoma is highly malignant. It develops from the epithelium of the mucosa but shows no tendency toward glandular formation. It is a fungating tumor, bleeding easily, and often first calls attention to itself by hemorrhage.

Carcinoma of the small intestine metastasizes early, and metastases are found in about one third of the cases at the time of operation. The sites of metastasis in the order of frequency are: mesenteric lymph nodes, peritoneum, liver, lungs and long bones.

It is interesting to conjecture why the small intestine, which is so much longer than the stomach and large intestine combined, is so much less frequently the site of carcinoma. Rankin and Mayo [3] suggested that the alkalinity and fluidity of the contents of the small bowel, as well as the absence of abrupt bends, may be the explanation.

Sarcoma.—Sarcoma of the small intestine occurs often enough to deserve widespread recognition. In 1934, Boyce and McFetridge [5] collected over 300 cases from the literature. In an earlier study, Corner and Fairbank [6] reviewed 103 cases of sarcoma of the intestinal tract and found that 63 per cent of the tumors were in the small intestine, the largest number being in the ileum. We differentiate here the true sarcoma from the lymphosarcoma, which is better termed "lymphoblastoma" to avoid confusion.

Ewing stated that a sarcoma may arise from any mature mesoblastic tissue, which in the small intestine includes the submucosa, the subserous connective tissue and the muscular coats of the intestinal wall. Histologically this accounts for the finding of fibrosarcoma and leiomyosarcoma as the most frequent types of sarcoma of the small bowel.

Lymphoblastoma, or lymphosarcoma,[7] is one of the most frequently encountered malignant tumors of the small intestine. The extensive lymphatic development of the small bowel probably renders it peculiarly susceptible to this disease. Ullman and Abeshouse,[8] in 1932, in a comprehensive review of lymphosarcoma of the intestinal tract, brought the total number of reported cases up to 375. Lymphoblastomas occur at any age but are especially frequent in the fourth and fifth decades of life. A large proportion of them are found in the terminal portion of the ileum.

BENIGN TUMORS

Adenoma.—The simple adenoma is the most frequently found benign tumor of the small intestine. In Raiford's series there were 15 adenomas, 10 of which were located in the ileum. Histologically the adenoma consists of soft masses of glandular tissue with a connective tissue stroma which is probably derived from the submucosa. The glandular tissue shows no evidence of malignant change, and its continuity with the normal mucosa can readily be traced.

Adenomas are usually single and small, but they sometimes occur in great numbers, as in multiple polyposis.[9] In most cases the adenoma is not of great clinical significance except when it is the cause of

5. Boyce, F. F., and McFetridge, E. M.: Primary Sarcoma of Intestine, Internat. S. Digest **17**:131, 1934.

6. Corner, E. M., and Fairbank, H. A. T.: Sarcomata of the Alimentary Tract, Tr. Path. Soc. London **56**:20, 1905.

7. Mayo, C. W., and Robins, C. R., Jr.: Lymphosarcoma, S. Clin. North America **15**:1163, 1935.

8. Ullman, A., and Abeshouse, B. S.: Lymphosarcoma of Small and Large Intestine, Ann. Surg. **95**:878, 1932.

9. Gatersleben, H.: Polyposis of Small Intestine, Deutsche Ztschr. f. Chir. **245**:628, 1935.

obstruction, intussusception or hemorrhage. Divergent theories are held as to the origin of adenomas, that is, as to whether they are the result of inflammatory changes or are primarily neoplastic. Although it seems well established that malignant disease frequently complicates multiple polyposis, it is debatable whether malignant changes can occur in the simple adenoma.

Fibroma.—Fibromas [10] are extremely rare in the small intestine, there being fewer than 40 reported cases in the literature. They arise from the submucosa or from the subserous connective tissue. While a few such tumors have occurred in children, the great majority of them have been found in persons in the fifth and sixth decades. Fibromas are usually small and rarely cause symptoms.

Leiomyoma.—Leiomyomas are among the more frequently reported tumors of the small intestine. They are found in the small and large bowel with equal frequency. King [10] collected 45 cases from the literature in 1917, but many more have been described since that time. They occur at all ages. In the small intestine the most frequent site is the ileum and the next most frequent the jejunum. They occur least often in the duodenum.

Leiomyomas usually develop from the internal or external muscular coats of the intestinal wall. Theoretically, they may arise also from the muscularis mucosae and from the arterioles, but this has not been established. They form predominantly internal or external tumors with reference to the lumen. They are slowly growing, but they may develop into huge masses. Histologically, leiomyomas consist of whorls of hypertrophied smooth muscle cells arranged in interlacing bundles supported by a connective tissue framework. They have a tendency toward hemorrhagic degeneration, which accounts for the frequent bleeding associated with the condition.

Lipoma.—Lipomas [11] are seldom seen except incidentally at the operating table or at necropsy. They are notable for their benign and innocuous nature, but occasionally their surfaces may become ulcerated and extensive bleeding may result. Microscopically, they reveal masses of the adult type of fat cells surrounded by delicate strands of connective tissue. Spontaneous expulsion of pedunculated lipomas has been reported.

Hemangioma.—Hemangiomas of the small intestine are rare but interesting tumors. Helvestine [12] described 14 cases found in the litera-

10. King, E. L.: Benign Tumors of the Small Intestine, Surg., Gynec. & Obst. **25**:54, 1917.

11. Comfort, M. W.: Submucous Lipomata of the Gastrointestinal Tract, Surg., Gynec. & Obst. **52**:101, 1931.

12. Helvestine, F., Jr.: Hemangiomatosis of the Intestines, Ann. Surg. **78**:42, 1923.

ture and 1 of his own. These tumors arise from blood vessels in the submucosa. Histologically they are composed of endothelium-lined spaces filled with blood and fibrin and supported by a connective tissue framework. They are described as being capillary or cystic, depending on the size and caliber of the vessels involved. They are of interest clinically because they may cause extensive and uncontrollable hemorrhage. Bleeding high in the small intestine may simulate a bleeding peptic ulcer,[13] while bleeding in the lower portion of the small intestine may arouse suspicion of a malignant growth.

Chylangiomas[14] are similar to hemangiomas in histologic structure except that instead of containing blood and fibrin they are filled with a gelatinous, pink-staining material derived from lymph. They originate from the lymphatic plexus of the submucosa.

Carcinoid, or Argentaffin Tumor.—The occurrence of carcinoid tumors in the small intestine has frequently been described. The report by Cooke[15] on this subject should be consulted. These tumors resemble carcinoma superficially but differ in these important respects: They show no intracellular changes, they have no tendency toward glandular formation, and they do not metastasize. They are not of great interest clinically because of their small size, being rarely more than 1 or 2 cm. in diameter. Large carcinoids have been found in the appendix.

Rare Tumors.—Aberrant pancreatic rests[16] are tiny benign tumors, 1 or 2 cm. in diameter, which receive their name from the fact that their histologic picture is strikingly similar to that of normal pancreas except that islands of Langerhans may be absent. It is probable that they develop from misplaced embryonal tissue.

Intestinal cysts are occasionally reported, but they are extremely rare. We distinguish here between true intestinal cysts and mesenteric cysts, which are not infrequent. Cystic pneumatosis[17] is a condition found in the Orient. In this disease gas-filled cysts of varying size are found, due to penetration of intestinal gas through tiny weak points in the bowel wall. The condition subsides spontaneously if let alone.

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13. Dudley, H. D.: Vascular Tumors of Small Intestine with Symptoms Simulating Peptic Ulcer, S. Clin. North America **14**:1331, 1934.

14. Naumann, H.: Chylangioma Cavernosum and Cysticum of the Ileum, Arch. f. klin. Chir. **147**:314, 1927.

15. Cooke, H. H.: Carcinoid Tumors of the Small Intestine, Arch. Surg. **22**: 568 (April) 1931.

16. Simpson, W. M.: Aberrant Pancreatic Tissue: Analysis of One Hundred and Fifty Human Cases, with Report of a New Case, in Contributions to Medical Science, Dedicated to Aldred Scott Warthin, Ann Arbor, Mich., George Wahr, 1927, p. 435.

17. Bubis, J. L., and Swanbeck, C. E.: Gas Cysts of the Intestine, Ann. Surg. **75**:620, 1928.

All types of benign and malignant tumors of Meckel's diverticulum have been reported, but they are obviously rare. Nygaard and Walters [18] collected 17 cases from the literature and added 3 of their own.

Secondary Tumors.—The small intestine is often involved in malignant tumors, which may originate in the stomach, colon, ovary or other abdominal organ. This involvement may be by direct extension or by metastasis.

CLINICAL ASPECTS

As we have mentioned, the diagnosis of tumor of the small intestine is made with difficulty. Often the finding of this condition at the operating table comes as a complete surprise to the surgeon. In reviewing a case the surgeon will frequently find that the clinical signs had pointed definitely to a disease of the small intestine but had not been so interpreted because of the relative infrequency of such a condition and the confusing similarity of the symptoms to those of other abdominal diseases. We believe that if the existence of this condition is kept in mind a correct diagnosis can be made in a fair percentage of cases.

The symptoms and clinical signs of the disease are due to changes in the mechanics of gastrointestinal function resulting from the presence of the tumor and also to the effect of the pathologic process on the general condition of the patient. In general, the symptoms vary according to the location of the tumor, its type, whether benign or malignant, and, in the latter instance, the degree of malignancy. The location and effect of metastases also play a part in the disease picture.

The symptoms are usually those of intestinal obstruction and may be acute, chronic or intermittent. It must be kept in mind, however, that a complication, such as perforation or hemorrhage, may be the first indication of the existence of the disease. Pain is the most frequent complaint; it is colicky and may be mild or severe. Nausea and vomiting are often present, especially in cases of tumor of the duodenum; if the tumor is in the jejunum or the ileum these symptoms appear later. There is often a loss of weight and strength, which is more marked if the tumor is malignant. There may be a change in intestinal habits, such as alternating attacks of diarrhea and constipation.

In the absence of complications there are few clinical findings on physical examination. The most frequent findings on palpating the abdomen are tenderness and a sensation of fulness to the examining finger. In a small proportion of cases there is a definite mass, which constitutes the most valuable single sign of tumor. Distention of the abdomen may be present. A succussion splash may be elicited. Blood,

18. Nygaard, K. K., and Walters, W.: Malignant Tumors of Meckel's Diverticulum, Proc. Staff Meet., Mayo Clin. **11**:504, 1936.

gross or occult, may be present in the stool or vomitus. In cases in which there is frequent vomiting, such as occurs with tumors high in the small intestine, dehydration and alkalosis are present, as well as hypochloremia and nitrogen retention. In periampullary tumors, jaundice simulating that associated with carcinoma of the head of the pancreas may be present.

With the onset of intestinal obstruction there arises the familiar picture of pain, distention, vomiting, constipation and perhaps visible peristaltic waves and signs of shock. When intussusception is present (and we must emphasize the frequent complicating of these tumors by intussusception [19]) one may find pain, characterized by sudden onset, accurate localization and long duration if not relieved, vomiting and the appearance of an elongated mass. Bloody stools may be passed.

Cases in which there is a gradual development of symptoms indicative of intestinal disturbance offer the surgeon sufficient time to make a correct diagnosis. In other cases, in which one is confronted with obvious peritonitis without sufficient antecedent history to make a correct diagnosis, the signs may point to appendicitis, perforated or bleeding ulcer or cholecystitis and may tax the diagnostic skill of the surgeon to the utmost.

Roentgenograms are not as helpful in cases of tumor of the small intestine as they are in cases of tumor elsewhere, on account of the great length of the intestine and the difficulty of filling it homogeneously. However, the finding of dilatation, filling defects, indentations due to constriction or evidences of acute or chronic obstruction offers assistance to the diagnostician.[20] Negative results from roentgen examination do not rule out tumor of the small intestine, but positive results are of definite value.[21]

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19. Fiske, F. A.: Intussusception Due to Intestinal Tumors, Ann. Surg. **106**: 221, 1937.

20. Soper, H. W.: Roentgen Ray Diagnosis of Lesions of the Small Intestine, Am. J. Roentgenol. **22**:107, 1929.

21. Ackerman, L. V.: Cavernous Hemangioma of the Small and Large Bowel, Am. J. Cancer **30**:753, 1937. Rankin, F. W., and Grimes, A. E.: Small Bowel Tumors, South. Surgeon **6**:280, 1937. Nickerson, D. A., and Williams, R. H.: Malignant Tumors of the Small Intestines, Am. J. Path. **13**:53, 1937. Liccione, W. T.: Malignant Tumors of Meckel's Diverticulum, Am. J. Surg. **34**:103, 1936. Doub, H. P., and Jones, H. C.: Primary Malignant Tumors of the Small Intestine, Radiology **26**:209, 1936. Klopp, E. J., and Crawford, B. L.: Leiomyoma of the Small Intestine, Ann. Surg. **101**:726, 1935. Kirshbaum, J. D.: Submucous Lipomas of the Intestinal Tract as Cause of Intestinal Obstruction, ibid. **101**:734, 1935. Joyce, T. M.: Tumors of the Small Intestine, ibid. **100**:949, 1934. Moore, R. H., and Schmeisser, H. C.: Benign Tumors of the Small Intestine, South. M. J. **27**:386, 1934. Prey, D.; Foster, J. M., Jr., and Dennis, W.: Primary Sarcoma of the Duodenum: Report of a Case, Arch. Surg. **30**:675 (April) 1935.

(Footnote continued on next page)

REPORT OF CASES

CASE 1.—M. F., a 50 year old white woman, was admitted to the surgical service on Sept. 14, 1932, with the complaint of generalized abdominal pains of several hours' duration. She had not had any previous serious illness or operation. Four months previously she had begun to have attacks of abdominal distress without any real pain. A series of gastrointestinal roentgenograms at that time revealed no abnormality. Six hours before her admission to the hospital she was suddenly seized with sharp, cramplike generalized pains, most severe in the right lower quadrant of the abdomen. She was nauseated and vomited several times. There had been two normal bowel movements during the previous twenty-four hours.

Physical examination revealed the patient to be acutely ill. The temperature was 100.2 F., the pulse rate 64 and the respiratory rate 20. The upper respiratory passages, lungs and heart were normal. The abdomen was moderately rigid on both sides but was more so on the right; there were definite localized tenderness and rebound tenderness in the right lower quadrant. No masses could be felt. The leukocyte count was 11,200 per cubic millimeter, with 88 per cent polymorphonuclears and 12 per cent lymphocytes. Urinalysis revealed traces of albumin, occasional white blood cells and no casts.

On the basis of these findings a diagnosis of acute appendicitis was made.

The abdomen was opened through a lower right rectus incision with the patient under general anesthesia. A large amount of fluid and clotted blood was encountered, which was easily traced to a ruptured cystic mass attached to the ileum. Exploration revealed no involvement of the lymph nodes, and the viscera appeared free of metastasis. A resection of the involved loop of ileum was made, and a side to side anastomosis was performed.

The patient reacted well from the operation, and her subsequent course in the hospital was uneventful. She was discharged on the twentieth day after the operation.

Pathologic Report.—Gross Picture: The specimen consisted of numerous fragments of clotted blood and soft papillary tissue, some of which was free and much of which was attached to what appeared to be the wall of a cyst measuring approximately 7 by 5 cm. There was also submitted a small portion of ileum to which some papillary material, similar to that previously described, was attached on its peritoneal surface.

Histologic Picture: The tumor was cellular, with a somewhat hyaline stroma. The cells were essentially oval, with hyperchromatic nuclei and many atypical giant forms. Many mitotic figures were present, some of them multipolar. The diagnosis was leiomyosarcoma.

Forbus, W. D.: Argentaffin Tumors of the Appendix and Small Intestine, Bull. Johns Hopkins Hosp. **37**:130, 1925. Ritter, S. A.: Neuroblastoma of the Intestine, Am. J. Path. **1**:519, 1925. Bier, E.: Lymphosarcoma of the Small Intestine, S. Clin. North America **5**:93, 1925. Rankin, F. W.: Lymphosarcoma of the Small Intestine, Ann. Surg. **80**:704, 1924. Clark, E. D.: Carcinoma of the Small Intestine, Surg., Gynec. & Obst. **43**:757, 1926. Brown, A. J.: Vascular Tumors of the Intestines, ibid. **39**:191, 1924. Judd, E. S., and Rankin, F. W.: Hemangiomas of the Gastrointestinal Tract, Ann. Surg. **76**:28, 1922. Mills, R. W.: Radiological Diagnosis of Small Intestinal States, Am. J. Roentgenol. **9**:199, 1922. Goldsmith, R.: Leiomyosarcoma of the Jejunum, Ann. Surg. **104**:148, 1936. Charache, H.: Primary Lymphosarcoma, Am. J. Surg. **27**:171, 1935.

Follow-Up.—Examinations of the patient at intervals of six months have revealed no recurrence of the tumor. She was alive and well when last seen, one year prior to the time of writing.

CASE 2.—T. B., a 32 year old white woman, was admitted to the hospital on July 11, 1933, with the complaint of abdominal pains of one week's duration. Prior to the onset of the illness for which she sought admission she had always enjoyed good health. A week previously she had pains of moderate intensity in the lower portion of the abdomen. These persisted until the day of admission, when they

Fig. 1.—Leiomyosarcoma.

became more severe and seemed to localize in the right lower quadrant. She became nauseated and vomited frequently.

On examination the patient appeared acutely ill. The temperature was 104 F., the pulse rate 104 and the respiratory rate 24. Examination of the throat, lungs and heart revealed no abnormalities. Palpation of the abdomen revealed spasticity of both rectus muscles, especially of the right, and there was considerable distention. No masses could be felt. The leukocyte count was 9,800 per cubic millimeter, with 84 per cent polymorphonuclears and 16 per cent lymphocytes. Urinalysis revealed no abnormalities.

A tentative diagnosis of pelvic peritonitis, possibly due to adnexal disease, was made. The possibility of appendicitis was also considered. Supportive treatment for the purpose of localizing the peritonitis was instituted. However, the patient's condition became steadily worse during the next two days, and operative intervention was decided on.

With the patient under general anesthesia, a lower right rectus incision was made. When the peritoneal cavity was entered a large amount of purulent fluid was encountered. Exploration revealed a large, necrotic tumor of the ileum. The

Fig. 2.—Leiomyosarcoma.

appendix and adnexae were inflamed by contiguity. A resection of the involved loop of ileum was made, followed by an end to end anastomosis. The appendix was removed. The abdominal cavity was drained and closed.

The postoperative course was stormy during the next few days, but after a blood transfusion the patient improved steadily. She was discharged on the twenty-fifth day after the operation with the wound completely healed.

Pathologic Report.—Gross Picture: The specimen consisted of an irregular, somewhat conical mass 8 by 6 cm. The base was nodular and the free surface hemorrhagic, the remainder becoming whitish and interspersed with yellowish opaque areas. On cut section this appeared to be a well encapsulated smooth

tumor, the middle third being occupied by soft, reddish tissue. There were some areas which were yellowish and translucent.

Histologic Picture: There were marked proliferation, hyperchromatism and many variations in size of the cells. The general appearance of the cells suggested the whorls seen in uterine leiomyomas. Many atypical cell forms, however, were present, with evidence of very rapid cell division and some necrosis. The diagnosis was leiomyosarcoma.

Follow-Up.—The patient was last seen six months prior to the time of writing and has remained well. There has been no evidence of recurrence.

Case 3.—S. S., a 21 year old white man, was admitted to the medical service of Dr. S. P. Sobel on Dec. 3, 1935, with the complaints of shortness of breath and attacks of abdominal pains. There was no previous history of rheumatic fever. For the past eighteen months he had suffered attacks of abdominal pains associated with nausea and vomiting, which were not related to eating and were not relieved by medication. Recently the attacks had become more frequent and had lasted for days at a time. During the past year he had become aware also of increasing shortness of breath on exertion.

Physical examination revealed the patient to be orthopneic and cyanotic. The superficial veins were congested. The pulse showed auricular fibrillation, with a rate of about 112 beats per minute. The blood pressure was 124 systolic and 42 diastolic. The lungs showed dulness at both bases on percussion, and many moist rales were audible. The heart was enlarged along both borders, and over the mitral valve both systolic and diastolic murmurs were heard. A diastolic murmur was heard also over the aortic area. The liver was enlarged to 2 finger-breadths below the costal margin. No masses were felt in the abdomen. There was slight pitting edema of the lower extremities. The Wassermann and Kahn reactions were negative. The blood count and urinalysis revealed no abnormality.

A diagnosis was made of rheumatic heart disease with mitral and aortic valvular involvement, auricular fibrillation and myocardial failure. This was confirmed by electrocardiographic and roentgen examinations.

The patient was rapidly digitalized and made satisfactory progress during the next few days. One week after admission he was suddenly seized with an attack of cramplike abdominal pains. Examination of the abdomen showed that the liver had receded in size, but in the right lower quadrant there was a soft, tender, elongated mass. There was no fever, and the leukocyte count was 8,800, with a normal differential count. A series of gastrointestinal roentgenograms showed incomplete obstruction. Several diagnoses were offered, including mesenteric vascular thrombosis, volvulus, appendicitis and intussusception. After several days of observation the attack subsided spontaneously and was followed by several similar attacks of lesser intensity. Finally a severe attack occurred, with the appearance of a long, sausage-shaped mass in the right lower quadrant of the abdomen. On the basis of the recurrent nature of the attacks with the presence of the gradually extending mass, a diagnosis of ileocecal intussusception, probably caused by a tumor of the ileum, was made.

With the use of spinal anesthesia a right rectus incision was made. A large intussusception of the ileum through the ileocecal valve was found. This was carefully reduced, and the cause of the intussusception was found to be a pedunculated, ball-like tumor situated about 18 inches (45 cm.) from the cecal end of the ileum. The tumor-bearing portion of the ileum was resected and a side to side anastomosis created.

The patient made an uneventful recovery and on the twenty-sixth day after operation was transferred from the hospital to a home for convalescent patients with cardiac disease.

Pathologic Report.—Gross Picture: The specimen consisted of a resected portion of intestine, 10 cm. in length, apparently ileum. On the mucosal aspect there was an eccentrically situated tumor, 4 cm. in its largest diameter and roughly oval. It had a short, thick pedicle. The serosal aspect at the site of the tumor

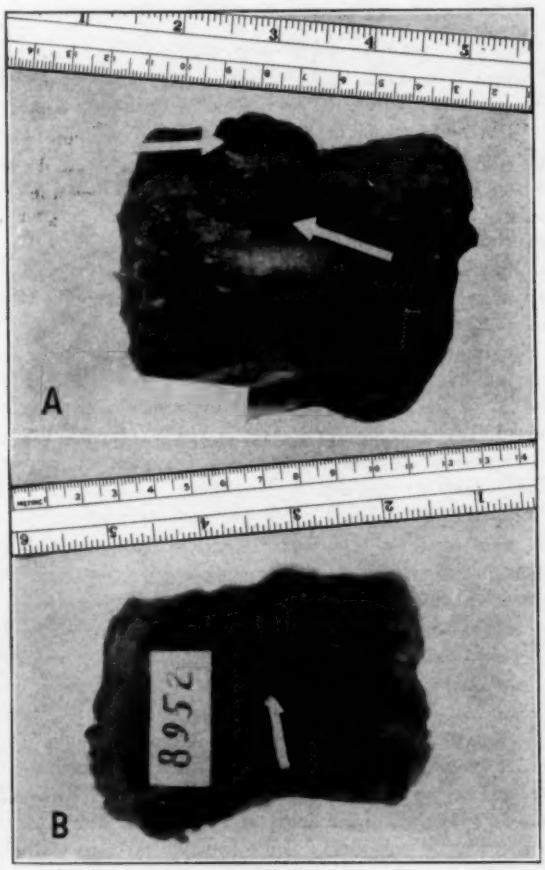

Fig. 3.—*A*, serosal surface of a leiomyoma. *B*, mucosal surface.

mass showed a peculiar puckering and several small nodules, 2 to 4 mm. in diameter.

Histologic Picture: The cells consisted of elongated oval to spindle-shaped cells with slightly hyperchromatic nuclei embedded in a rather dense, somewhat edematous stroma. There appeared to be no evidence of rapid cell division or other features pointing to malignancy. The diagnosis was leiomyoma.

Follow-Up.—The patient has been seen within recent months, and while the cardiac condition is still in evidence, there has been no recurrence of abdominal symptoms.

CASE 4.—R. E., a 23 year old white man, was admitted to the hospital on Nov. 22, 1936, with the complaint of generalized abdominal pains associated with nausea and vomiting. One year ago he had begun to have attacks of diarrhea accompanied by mild cramplike pains. These aroused no anxiety, and he gained several pounds in weight during this time. One week before admission he was seized with an attack of severe pains near the umbilicus. The following day diarrhea appeared, lasting twenty-four hours. After this he felt better except for mild pains which recurred at intervals. On the day prior to admission severe intermittent colicky pains again appeared, with nausea and vomiting.

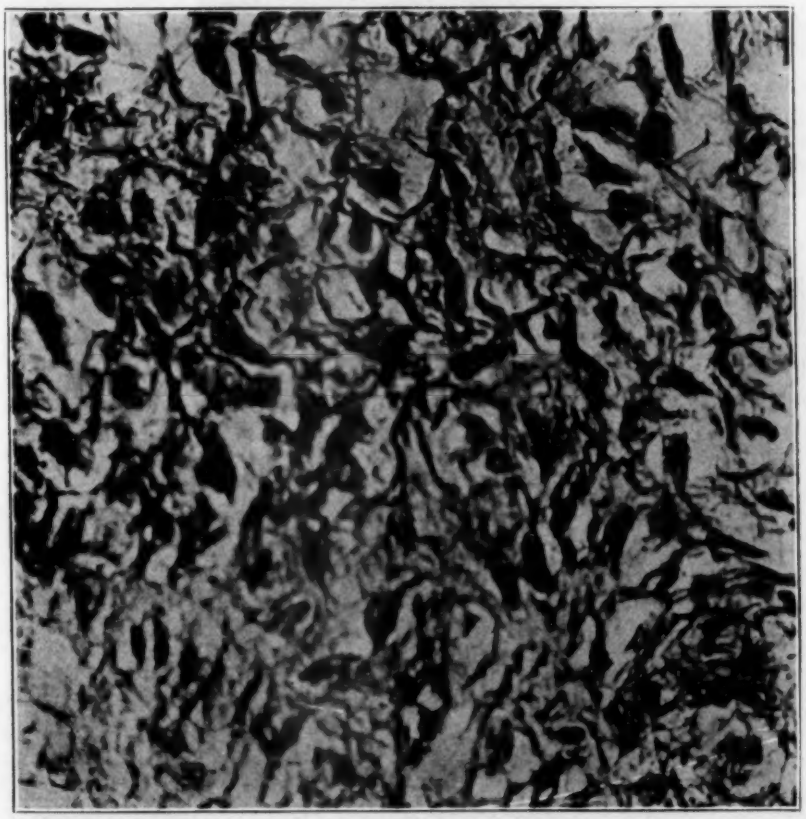

Fig. 4.—Leiomyoma.

The temperature on admission was 100.6 F., the pulse rate 68 and the respiratory rate 22. Examination of the nose and throat revealed no abnormalities. The lungs were clear to percussion and auscultation. The heart was normal. The abdomen was considerably distended, but no tenderness or rigidity was noted. No masses were felt. The leukocyte count was 10,700 per cubic millimeter, with band forms 8 per cent, polymorphonuclears 74 per cent, lymphocytes 16 per cent and monocytes 2 per cent. Urinalysis revealed no abnormalities. Roentgenograms showed marked gas distention of the small bowel, mainly in the left upper quadrant of the abdomen; with the patient in the erect posture, fluid levels were present. The stomach was distended and contained fluid. A diagnosis of intestinal obstruction high in the small bowel was made.

Fig. 5.—Leiomyoma. *A*, gross specimen; *B*, microscopic specimen.

With the use of spinal anesthesia a left upper rectus incision was made. When the peritoneal cavity was entered a large amount of serosanguineous fluid was encountered and distended loops of small intestine were seen. An oval tumor about the size of a golf ball was found attached to the upper portion of the ileum at the antimesenteric border by a narrow pedicle. The tumor was hemorrhagic and somewhat necrotic. It had rotated four times on its pedicle. There was an acute angulation of the bowel due to the pulling up of the tumor by adherent omentum, and this was the mechanism of the obstruction. The tumor was easily removed by clamping and ligating the base of the pedicle, and the serosal surface was covered over by a Lembert suture.

The patient made an uneventful recovery and was discharged from the hospital on the fourteenth day after the operation.

Pathologic Report.—Gross Picture: The specimen consisted of a pedunculated tumor mass 4 by 4 cm., attached to the mucosal aspect of the small intestine by a 2 cm. pedicle. The mass appeared well encapsulated and was firm. On section it was hemorrhagic in appearance, and the pedicle contained a small lumen. A small portion of the omentum was attached to the tumor. The general appearance suggested torsion and strangulation.

Histologic Picture: The appearance was that of degeneration with hemorrhagic infiltration of leiomyoma. The pedicle consisted of intestinal wall devoid of mucosa. There was a lumen in the pedicle, not lined by epithelium. The diagnosis was degenerated leiomyoma.

Follow-Up.—The patient was last seen three months prior to the time of writing and showed no evidence of recurrence.

CASE 5.—R. N., a 30 year old white woman, was admitted to the hospital on Sept. 30, 1932, with the complaint of frequent attacks of abdominal pains associated with nausea and vomiting. These attacks had begun six months previously and had been infrequent at first but recently had become a daily occurrence. Since the onset of this illness she had lost 20 pounds (9.1 Kg.).

On physical examination the patient looked emaciated and chronically ill. The temperature was 101.2 F.; the pulse rate was 120, and the respiratory rate was 22. Examination of the upper respiratory passages, the lungs and the heart revealed no abnormalities. The abdomen had a peculiar doughy resistance on palpation. On deep palpation there was slight tenderness in the right lower quadrant. No masses could be felt. No fluid wave was present. Vaginal examination showed the uterus to be retroverted, and the cervix revealed chronic endocervicitis. Laboratory examination revealed: hemoglobin, 73 per cent; leukocytes, 11,500 per cubic millimeter, with polymorphonuclears 77 per cent and lymphocytes 23 per cent. The urine was normal. Roentgenograms of the chest and a flat plate of the abdomen revealed no abnormalities. A series of cholecystograms showed that the gallbladder filled faintly with dye, probably owing to adhesions between it and the duodenum. No stones were present.

On the basis of these findings it was suspected that chronic peritonitis, possibly tuberculous, was present, and exploratory operation was advised.

Laparotomy was performed with the use of spinal anesthesia. A tumor mass was found attached to the upper portion of the jejunum, about 9 inches (23 cm.) from the fossa of Treitz. The omentum was adherent to the tumor. The mesenteric lymph nodes were enlarged, but the liver and other viscera appeared to be free of metastasis. A resection of the involved jejunum including about 3 inches (7.5 cm.) on either side of the tumor was performed, and the continuity of the intestine was restored by a side to side anastomosis.

The patient made an uneventful recovery from the operation and was discharged on the fifteenth postoperative day.

Pathologic Report.—Gross Picture: The specimen consisted of a 10 cm. portion of small intestine exhibiting on its mucosal aspect a solid oval tumor, approximately 3 by 2.5 cm. The mass was sessile and appeared to have penetrated the entire wall, involving a small mass of fat which was adherent to its serosal surface.

Histologic Picture: The cells consisted essentially of spindle and oval types, varying in size and exhibiting many degrees of polymorphism, hyperchromatism, giant nuclei and atypical mitosis. There was a fine connective tissue stroma which appeared to be well vascularized. The diagnosis was leiomyosarcoma.

Second Admission.—On August 29, 1937, five years after her discharge, the patient was readmitted. She stated that she had been well until six weeks previously, when attacks of abdominal pain accompanied by vomiting had returned. Her weight, which had increased from 101 to 128 pounds (46 to 58 Kg.) during this time, had fallen to about 113 pounds (51 Kg.) during the few weeks just past. She felt continually nauseated.

Physical examination gave essentially negative results except for the abdomen. On palpation the abdomen was distended and markedly tender. Irregular masses could be felt in the left lower quadrant. A diagnosis of subacute intestinal obstruction due to a recurrence of the tumor was made. After a week of observation with no amelioration of symptoms a blood transfusion was given. The following day exploratory operation was performed. A large, conglomerate mass of intestines was found, which was the seat of widespread sarcomatous involvement. Intervention was deemed inadvisable.

The patient rallied from the operation, but on the following day the temperature became elevated and signs of consolidation appeared at the bases of the lungs. The patient died on the third day after the operation.

Case 6.—S. R., a 9 year old girl, was admitted to the hospital on Aug. 5, 1936, with the complaints of progressive enlargement of the abdomen and persistent fever. The child had been well until the onset of the present illness, three months previously. At that time the mother noticed that the abdomen was becoming progressively larger, although there were no subjective complaints. Ten days before her admission to the hospital there was a sudden increase in the enlargement and the child began to vomit. The temperature rose to 101 F. The next day the vomiting ceased, but the fever persisted. The patient became pale and lost considerable weight.

Physical examination revealed marked pallor, a temperature of 100 F., a pulse rate of 120 and a respiratory rate of 36. There was no enlargement of the superficial lymph nodes. There was dulness on percussion at the bases of the lungs, with some diminution of the breath sounds. The heart was normal. Examination of the abdomen revealed marked distention and unusual prominence of the superficial veins. A large, irregular mass was palpable in the right lower portion of the abdomen. It was firm and could be displaced without pain. A fluid wave was present, with shifting dulness in the flanks. Laboratory examination disclosed: hemoglobin, 70 per cent; erythrocytes, 4,300,000 per cubic millimeter; leukocytes, 14,000 per cubic millimeter, with band forms 10 per cent, polymorphonuclears 74 per cent, lymphocytes 13 per cent and monocytes 3 per cent. The urine was normal except for occasional red and white blood cells. Roentgenograms revealed displacement of the ascending colon and cecum by a mass. An abdominal paracentesis was performed, and 1,000 cc. of a light coffee-colored fluid was removed.

On the basis of these findings lymphosarcoma, Hodgkin's disease and malignant tumor of the right ovary were considered.

Exploratory operation was performed with the patient under ether anesthesia. When the peritoneal cavity was entered it was necessary to evacuate about 6 quarts (5.6 liters) of turbid fluid. Several large tumor masses were encountered, the largest and apparently primary growth arising from the ileum. Several of these masses were amputated. The involved loop of bowel was delivered out of the wound and walled off with packing. As the condition of the patient suddenly

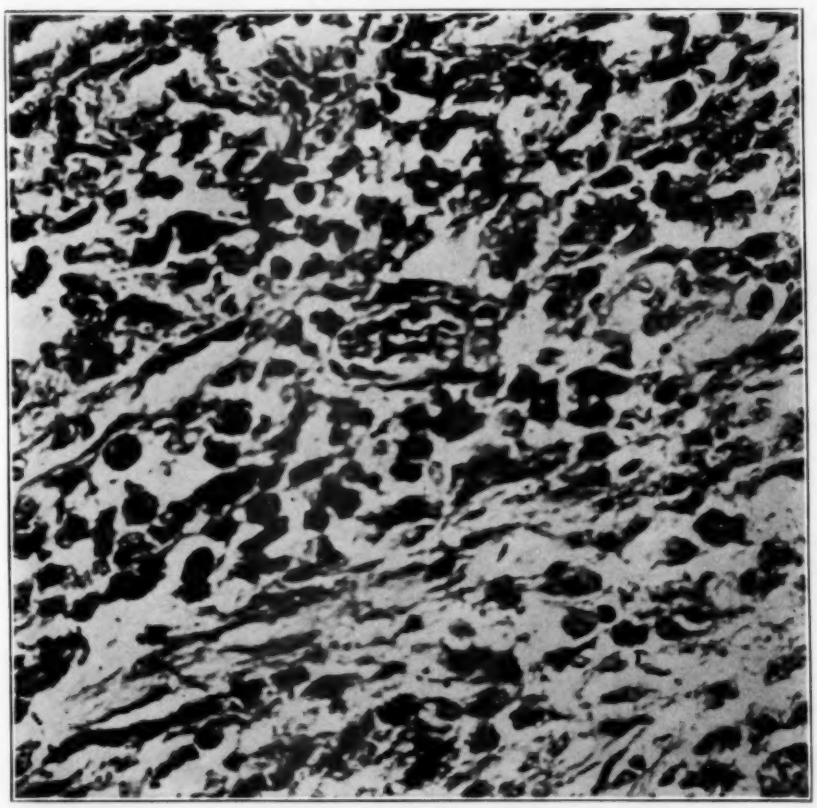

Fig. 6.—Leiomyosarcoma.

became critical at this point, the procedure was terminated with the expectation of resuming it later.

About an hour and a half after the operation the patient went into profound shock and died in spite of supportive measures.

Pathologic Report.—Gross Picture: The specimen consisted of many irregular fragments of whitish tissue, the largest measuring 8 by 4 cm.

Histologic Picture: The sections exhibited a marked cellular proliferation, the type of cell being round, with a large, pyknotic nucleus and scanty, faintly staining cytoplasm. Many of the cells were large and exhibited evidence of rapid cell division. The stroma was scanty and in some places edematous. The diagnosis was lymphosarcoma.

Case 7.—E. K., a 38 year old white woman, was admitted to the hospital on May 11, 1938, with the complaints of severe abdominal pains, nausea and vomiting for the past few hours. She stated that four months previously she had begun to have recurrent cramplike abdominal pains, especially in the left lower portion of her abdomen. She also became troubled by eructation, distention and increasing constipation. She vomited occasionally. Two weeks previously a barium sulfate enema had been given at another hospital and the results reported to be negative. A barium sulfate meal had been given also, but the report was not available. A few hours before admission she was suddenly seized with severe

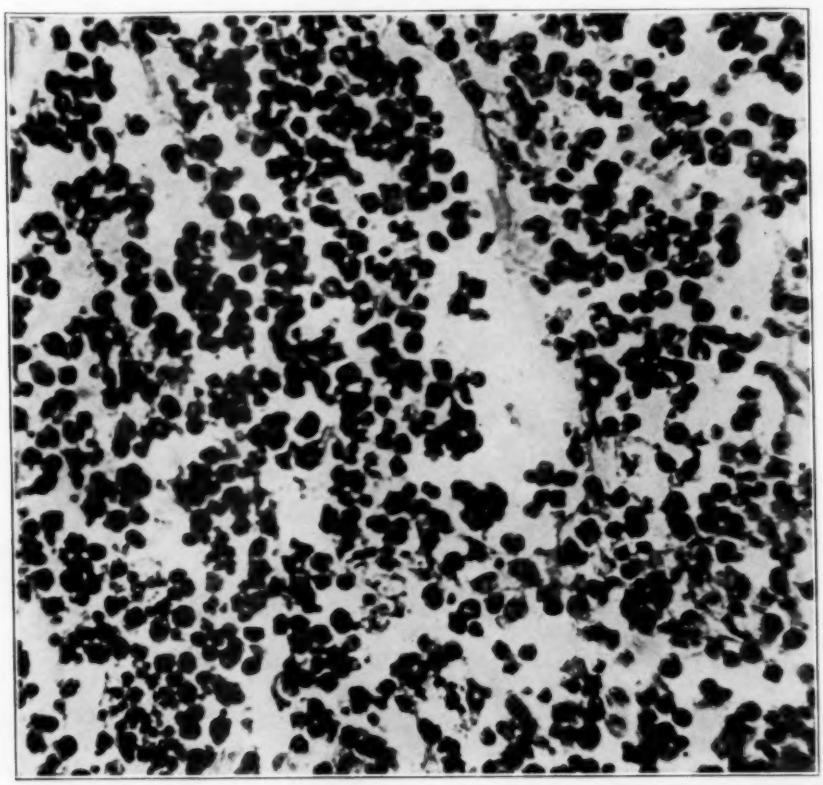

Fig. 7.—Lymphosarcoma.

abdominal pains in the right lower quadrant, radiating upward toward the epigastrium and also felt in the back and in the right shoulder. She vomited twice during this time.

Physical examination revealed the patient to be acutely ill. The temperature was 99.6 F. and the pulse rate 84. The heart and lungs were normal. The abdomen showed considerable distention, and there was rigidity of both rectus muscles, especially on the right side. There were tenderness on palpation and rebound tenderness, both more marked on the right side. Dulness of the liver was not obliterated. Vaginal examination gave negative results. During the examination there were recurrent exacerbations of the severe pains, with visible

Fig. 8.—Carcinoma of the jejunum: *A*, mucosal surface; *B*, microscopic section.

movements of distended loops of bowel. The leukocyte count was 9,400 per cubic millimeter, with the following differential count: band forms, 12 per cent; polymorphonuclears, 66 per cent; lymphocytes, 18 per cent, and monocytes, 4 per cent. The urine was normal.

The symptoms described by the patient, together with the physical findings and the negative roentgen reports on the large bowel suggested the diagnosis of an obstructive lesion of the small bowel, with an acute episode, possibly perforation, superimposed.

With the use of spinal anesthesia a right midrectus incision was made. When the peritoneal cavity was entered 2 liters of turbid fluid was encountered, which contained some barium. Particles of barium were also found covering the intestines. A tumor mass involving the jejunum was found with a perforation near its center. Numerous glands were found in the mesentery, but the liver and other viscera were not involved. A wide resection of the jejunum was made, and continuity was restored by a side to side anastomosis. A cigaret drain was placed in the pelvis.

The patient made an uneventful recovery from the operation and was discharged from the hospital on the fourteenth day after operation.

Pathologic Report.—Gross Picture: The specimen was a resected portion of small intestine, measuring 14 by 9 cm. It was open. In approximately the center of the bowel was an ulcerated mass measuring 6 cm. in diameter. The edges were raised, nodular and thickened. The floor was necrotic and hemorrhagic and exhibited near the center a 3 mm. perforation which extended through all the coats to the serosa. The wall was markedly thickened and indurated about the region of the ulcer. The overlying serosa was infiltrated and edematous. The remainder of the intestine showed no gross pathologic change. Several minute lymph nodes were found close to the mesenteric attachment.

Histologic Picture: The general microscopic picture and character of the mural infiltration suggested anaplastic carcinoma rather than sarcoma. The growth was probably one of the rare primary tumors of the small intestine. The diagnosis was anaplastic carcinoma.

Follow-Up.—In this case the patient shows no recurrence of symptoms at present.

SUMMARY

The types, clinical aspects and treatment of benign and malignant tumors of the small intestine are discussed. Seven cases are reported.

Dr. Joseph Felsen, Director of Laboratories and Research at the Bronx Hospital, permitted the use of the photographs, photomicrographs and pathologic reports.

PARTIAL AGENESIS OF THE CORPUS CALLOSUM

DIAGNOSIS BY VENTRICULOGRAPHIC EXAMINATION

ALONZO B. CASS, M.D.
AND
DAVID L. REEVES, M.D.
LOS ANGELES

Although Reil [1] described the first case of agenesis of the corpus callosum as early as 1812, the apparent rarity of the condition is indicated by the fact that Baker and Graves,[2] reviewing the literature in 1933, discovered only 81 reported cases, to which they added 1 of their own. Of the 82 cases, only 2 were reported in the United States. Archambault,[3] in 1911, described a case of complete agenesis. In the case reported by Baker and Graves the agenesis was partial.

Until the introduction of ventriculography in 1918 [4] and encephalography in 1919 [5] by Dandy there was no method of diagnosing the condition during life, and for this reason agenesis of the corpus callosum was invariably discovered unexpectedly at autopsy.

Apparently Guttmann [6] made the first encephalographic study of this condition in 1929. His description of the encephalographic picture was typically that of agenesis of the corpus callosum, but the characteristic changes in the encephalogram were not recognized and the diagnosis was not made during the life of the patient. The anomaly was discovered accidentally at postmortem examination.

The first published report of the diagnosis of agenesis of the corpus callosum by encephalographic methods was made by Davidoff and

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From the Children's Hospital.

1. Reil, J.: Mangel des mittleren und freien Theils des Balkens in Menschengehirn, Arch. f. d. Physiol. **11**:341, 1812.

2. Baker, R., and Graves, G.: Partial Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. **29**:1054 (May) 1933.

3. Archambault, LaSalle: A Contribution to the Anatomy and Pathology of Agenesia of the Corpus Callosum, Albany M. Ann. **32**:513, 1911.

4. Dandy, W. E.: Ventriculography, Ann. Surg. **68**:5, 1918.

5. Dandy, W. E.: Roentgenography of the Brain After the Injection of Air in the Spinal Canal, Ann. Surg. **70**:397, 1919.

6. Guttmann, L.: Ueber einen Fall von Entwicklungsstörung des Gross- und Kleinhirns mit Balkenmangel, Psychiat.-neurol. Wchnschr. **31**:453, 1929.

Dyke [7] in a paper read before the American Association of Neuropathologists, Dec. 28, 1933. Hyndman and Penfield [8] reported 2 cases at the sixtieth annual meeting of the American Neurological Association, in June 1934, and added 3 more in an article published June 1937.

Interestingly, in each of these reports the clinical diagnosis in the first cases was cyst of the septum pellucidum. The first patient of Dyke and Davidoff [7] was a white girl aged 6 years. An encephalogram taken Dec. 11, 1930 was typical of agenesis of the corpus callosum, but the diagnosis was not made until autopsy, death having followed a small osteoplastic craniotomy on the right side, performed on Oct. 24, 1933 for a supposed cyst of the cavum of the septum pellucidum. At the time the encephalogram was taken, the large collection of air seen between the lateral ventricles, which included the space normally occupied by the third ventricle, was interpreted as filling the cavity of the septum pellucidum and the cavum Vergae, the walls of which were ruptured during the procedure, allowing the escape of fluid and permitting filling with air. Moreover, the diminution of epileptic seizures during the subsequent two years seemed to verify the assumption that the cyst had ruptured during the insufflation with air.

An encephalogram was taken of their third patient prior to verification of the lesion of the first patient, and again operation was undertaken on the basis of a mistaken roentgen diagnosis of cyst of the cavum septi pellucidi. After the postmortem examination of the first patient, of course the diagnosis of agenesis of the corpus callosum in the case of the third patient became evident.

Similarly, the picture in the first case reported by Hyndman and Penfield [8] "indicated an abnormal condition in the midline, and led us at first to suspect a cyst of the cavum septi pellucidi." It was for this reason that the patient, a child, was operated on; the possibility of partial agenesis of the corpus callosum was not considered.

Because of a similar ventricular abnormality in their second case. a small osteoplastic flap was turned over the longitudinal fissure. When the right hemisphere was retracted from the falx, the unexpected condition was revealed. Instead of the corpus callosum, only a translucent membrane bridged the bottom of the fissure. The corpus callosum and the septum pellucidum seemed to be completely absent, but no other gross abnormality, except lateral displacement of the basal ganglions of each side and obvious enlargement of the ventricular system, was observed.

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7. Davidoff, L. M., and Dyke, C. G.: Agenesis of the Corpus Callosum: Its Diagnosis by Encephalography; Report of Three Cases, Am. J. Roentgenol. **32**:1, 1934.

8. Hyndman, O. R., and Penfield, W.: Agenesis of the Corpus Callosum: Its Recognition by Ventriculography, Arch. Neurol. & Psychiat. **37**:1251 (June) 1937.

As a result of these findings and in view of the characteristic encephalographic picture, the condition in their 3 subsequent cases was immediately recognized.

Prior to this time, attention had been called to congenital cerebral cysts of the cavum septi pellucidi and the cavum Vergae in Dandy's interesting paper,[9] but the differences in the pneumographic features of these cysts and agenesis of the corpus callosum had not yet been appreciated.

Since the collection of 82 cases by Baker and Graves,[2] 17 additional cases have been reported. These include the 3 cases of Davidoff and Dyke and the 5 of Hyndman and Penfield. In 1 other, mentioned by Hyndman and Penfield[8] and included by Dandy[10] in Dean Lewis' "Practice of Surgery," the ventriculogram showed a congenital deformity of the brain which was without doubt agenesis of the corpus callosum. The other cases are those reported by de Morsier and Mozer,[11] and the 6 reported by Juba,[12] Regirer[13] and Segal[14] (2 by each author).

To these we add our present case, which brings the total of those reported to 100. Ours is the ninth instance of this anomaly in which the condition was diagnosed during the patient's life by cerebral pneumographic examination, and the diagnosis was made at the earliest age on record.

EMBRYOLOGY

Retzius has demonstrated the corpus callosum as an outgrowth of the lamina terminalis. Its formation occurs during the third and fourth months of fetal life, progresses concomitantly with the development of the hippocampal commissure and the septum pellucidum and becomes complete by the fifth month.[15]

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9. Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle), Arch. Neurol. & Psychiat. **25**:44 (Jan.) 1931.

10. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 12, p. 331.

11. de Morsier, G., and Mozer, J. J.: Agénésie complète de la commissure calleuse et troubles du développement de l'hémisphère gauche avec hémiparésie droite et intégrité mentale (Le syndrome embryonnaire précoce de l'artère cérébrale antérieure), Schweiz. Arch. f. Neurol. u. Psychiat. **35**:64 and 317, 1935.

12. Juba, A.: Ueber einen mit Cystenbildung des Gehirns, Heterotopie der Plexus Choriodei und Mikrogyrie verbundenen Fall von vollständigem Balkenmangel, Arch. f. Psychiat. **102**:731, 1934; Ueber vollständigen Balkenmangel bei einem 39 jährigen geistig normalen Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:45, 1936.

13. Regirer, A.: Ueber zwei Fälle von Balkenlosigkeit am menschlichen Gehirn, Schweiz. Arch. f. Neurol. u. Psychiat. **36**:306, 1935; **37**:99, 1936.

14. Segal, M.: Agenesis of the Corpus Callosum in Man, South African J. M. Sc. **1**:65, 1935.

15. Keibel, F., and Mall, F.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, pp. 91-95.

As is shown so well by the diagrams of Hyndman and Penfield,[8] the anlage of the corpus callosum becomes visible during the third month of intrauterine life as a cephalic projection from the lamina terminalis. As this anterior aspect of the corpus callosum develops, it progresses posteriorly over the fimbria and the thalamus. In its posterior progress it carries the septum pellucidum beneath it. This triangular structure subsequently becomes bounded by the corpus callosum anteriorly and superiorly, the hippocampal commissure of the crura of the fornix posteriorly and the lamina rostralis inferiorly.

From such embryonic development, it is obvious that associated structures may well be affected by agenesis of the corpus callosum.

The development of the corpus callosum in higher mammals has led to a zoologic division of this highest class of vertebrates into two subclasses, the callosal and the acallosal mammals. The structure reaches its highest degree of development in the primates and becomes little more than a membranous structure in the lowest group of callosal mammals. As has been pointed out by Cameron,[16] the formation of convolutions in the brain increases its total volume three times, and the size of the corpus callosum is always proportional to this volume.

As might have been expected, absence of the corpus callosum in animals has been reported. King and Keeler [17] discovered agenesis of the corpus callosum in a strain of house mice, many of which showed abnormal absence of the rods in the retina. These authors found that the agenesis was familial and was probably inherited as a unit character. In the animals studied by them the corpus callosum was either present or entirely absent. A superficial examination of the reactions of the mice with and those without a corpus callosum revealed nothing distinguishing. Tumbelaka [18] has described total agenesis of the corpus callosum in a cebus monkey.

AGE INCIDENCE

In the majority of cases this condition has been disclosed at autopsy in persons less than 10 years old. Hayek [19] reported partial agenesis in

16. Cameron, J. L.: The Corpus Callosum: A Morphological and Clinical Study, Canad. M. A. J. **7**:609, 1917.

17. King, L. S., and Keeler, C. E.: Absence of the Corpus Callosum: A Hereditary Brain Anomaly of the House Mouse; Preliminary Report, Proc. Nat. Acad. Sc. **18**:525, 1932. King, L. S.: Absence of the Corpus Callosum: Hereditary Defects of the Corpus Callosum in the Mouse, Mus Musculus, J. Comp. Neurol. **64**:337, 1936.

18. Tumbelaka, R.: Das Gehirn eines Affen worin die interhemisphäriale Balkenverbindung fehlte, Folia neurobiol. **9**:1, 1935.

19. Hayek, H.: Ueber einen Fall von Hypoplasie des Balkens an einem in situ gehärteten Gehirn eines Neugeborenen, Virchows Arch. f. path. Anat. **273**:767, 1929.

a newborn infant, de Crinis [20] complete agenesis in an infant 2 weeks old and de Lange [21] complete agenesis in a baby aged 5 months who had died of pneumonia. The anomaly has been found at almost all ages, the upper limit being represented by 2 patients who died, respectively, at the ages of 72 [22] and 73 years.[23]

CAUSES OF AGENESIS OF THE CORPUS CALLOSUM

The causes suggested for developmental peculiarities in general have been advocated in cases of this anomaly. In Banchi's case [23] absence of the corpus callosum was unassociated with other important anomalies. For this reason he claimed that the condition was the result of a circumscript pathologic process in the mesial side of the embryonic lamina terminalis. Such a simple explanation is, of course, untenable in other cases, for so many anomalies are present that the entire brain must be considered pathologic.

Stoecker's patient [24] died of juvenile dementia paralytica (syphilis was probably the cause), and Landsbergen [25] expressed the belief that the presence of hereditary syphilis was probable in his case.

Several authors have explained the origin on the basis of the rather constantly present hydrocephalus, which enlarges the distance between the hemispheres and prevents the crossing. They have interpreted the hydrocephalus on the basis of ependymitis, and when this condition could not be found they assumed that it had been present formerly.

De Lange [21] pointed out that if hydrocephalus is not already present during the third month of fetal life it cannot account for the absence of the corpus callosum, and she proposed a lesion of the germ as the cause.

Because the corpus callosum normally forms the roof of the lateral ventricles, Cameron [16] stated that the hydrocephalus is more apparent than real.

At all events, it seems hardly possible that hydrocephalus can precede the formation of the corpus callosum.

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20. de Crinis, M.: Ueber einen Fall von Balkenmangel, J. f. Psychol. u. Neurol. **37**:443, 1928.

21. de Lange, C.: On Brains with Total and Partial Lack of the Corpus Callosum and on the Nature of the Longitudinal Callosal Bundle, J. Nerv. & Ment. Dis. **62**:449, 1925.

22. Poterin-Dumontel: Absence congénitale du corps calleux sans troubles fonctionnels durant la vie, Compt. rend. Soc. de biol. **4**:94, 1863; Gaz. d. hôp. **36**: 47, 1863.

23. Banchi, A.: Studio anatomico di un cervello senza corpo calloso, Arch. ital. di anat. e di embriol. **3**:658, 1904.

24. Stoecker, W.: Ueber Balkenmangel im menschlichen Gehirn, Arch. f. Psychiat. **50**:543, 1912.

25. Landsbergen, F.: Ueber Balkenmangel, Ztschr. f. d. ges. Neurol. u. Psychiat. **11**:515, 1912.

Chemical toxins have been proposed as an etiologic factor, but there is no substantial evidence of their influence.

Whatever the cause in any particular case may be, it seems obvious that this anomaly is due to arrest of the normal development of the callosal body, which of course may occur at any stage.

ANOMALIES ASSOCIATED WITH AGENESIS OF THE CORPUS CALLOSUM

Certain anomalies of the brain are almost constantly associated with absence of the corpus callosum. Dilatation of the posterior horns of the lateral ventricles is most frequently encountered. With this dilatation occurs a thinning of the walls of the posterior horns. The calcarine and parieto-occipital sulci are prevented from joining by the interposition of a superficial gyrus.

On the mesial aspect of the cerebral hemisphere the sulci possess a radiating arrangement. Prior to the formation of the corpus callosum, similar shallow sulci, radially arranged, are frequently visible on the mesial aspects of the embryonic cerebral hemispheres. These are felt to be natural, though transitory, structures. For this reason it would seem that the radial arrangement of the convolutions and sulci of the mesial aspect of the brain in cases of agenesis of the corpus callosum represents a similar preservation of this primitive transitory arrangement occurring prior to the third month of fetal life, before the formation of the corpus callosum. This probability is supported not only by the fact that the radial arrangement of the convolutions and sulci is preserved in cases of complete agenesis of the corpus callosum but by the observation that when partial agenesis exists such radial arrangement is absent dorsal to the partially formed corpus callosum and is again preserved where the latter structure has failed to develop.

In most cases the condition is associated with some other anomaly, such as microcephaly, porencephaly, polygyria, absence of the olfactory nerves, incomplete separation of the frontal lobes, hydrocephalus or an enlarged anterior commissure.

In the study of her case, Lange [21] found inhibition in development of the cortex revealed by the presence of the internal granular area throughout in the brain. Moreover, the granularis interna in the area of the calcarine fissure was not divided into the three layers. According to Brodmann,[26] this separation occurs normally in a 7 month fetus.

Lipoma associated with agenesis of the corpus callosum has been reported on numerous occasions. Huebschmann [27] described an instance

26. Brodmann, K.: Vergleichende Lokalizationslehre der Grosshirnrinde, Leipzig, J. A. Barth, 1909.

27. Huebschmann: Ueber einige seltene Hirntumoren: III. Lipom des Balkens bei partiellem Balkenmangel, Deutsche Ztschr. f. Nervenh. **72**:222, 1921.

of partial absence in which a lipoma was situated on the genu of the corpus callosum, and Huddleson,[28] a case in which a lipoma was situated between the frontal lobes.

Bodily defects accompanying agenesis of the corpus callosum have only occasionally been reported. These have included cleft palate and harelip, heteropia of the brain substance, cryptorchidism and malposition of the stomach high in the thorax. Physical development is often above the average in patients with absence of the corpus callosum.

Complete agenesis of the corpus callosum has been observed in more than half the cases. The analysis of Mingazzini [29] revealed that of 71 cases complete agenesis was present in 43 and partial agenesis in 28.

Forms of partial agenesis of the corpus callosum may vary from one in which the structure is complete except for a defective splenium to one in which there is only a rudimentary bundle of fibers in the region of the genu, with consequent absence of the septum pellucidum.

On the basis of the embryonic period in which arrest occurs, Bruce [30] divided defects of the corpus callosum into four main types. When the development continues until the end of the fourth month the genu and the posterior extension of the corpus callosum will be present. If development ends at the fourth month the anterior commissure will be formed by union of the laminas of the septum pellucidum at their anterior inferior angles. When arrest occurs prior to the fourth month the corpus callosum, septum pellucidum, lyra of the fornix and anterior commissure will be absent, but the hemispheres will be divided. If arrest begins during the first three weeks of embryonic life not only will the corpus callosum, septum pellucidum, fornix, velum interpositum and anterior commissure be absent, but the cerebrum will consist of a single vesicle and the ventricle of a single cavity.

FUNCTION OF THE CORPUS CALLOSUM

As a result of their experimental work on monkeys, Lafora and Prados [31] found that, depending on whether the location is anterior or posterior, section of the corpus callosum was followed by paralysis of the upper or of the lower extremities. Moreover, they discovered that section on either the right or the left side was followed by a series of phenomena identical with those of crossed hemiplegia.

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28. Huddleson, J. H.: Ein Fall von Balkenmangel mit Lipomentwicklung im Defekt, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:177, 1928.

29. Mingazzini, G.: Der Balken: Eine anatomische, physio-pathologische und klinische Studie, Berlin, Julius Springer, 1922.

30. Bruce, A.: On the Absence of the Corpus Callosum in the Human Brain with the Description of a New Case, Brain **12**:171, 1889.

31. Lafora, G. R., and Prados y Such, M.: Investigaciones experimentales sobre la function del cuerpo calloso, Siglo méd. **69**:169, 1922.

Later work by Seletzky and Gilula [32] on dogs and rabbits revealed that section of the hindpart of the corpus callosum caused little disturbance, except slight ataxia of the extremities. Section of the anterior or the middle part of the corpus callosum resulted in a disturbance of sensibility, sometimes in all the extremities, sometimes in only some and sometimes in the body or trunk. The gait became ataxic. Disturbance of the sense organs on the side of the section occurred, resulting in loss of hearing, sight or the sense of smell. Occasionally the animals tended to move in circles. Interestingly, all of the symptoms previously described disappeared after a variable interval, and no further abnormalities were observed. This important fact has been overlooked by many authors.

According to Mingazzini,[29] one differentiates internal, mesial and inferior fibers in the corpus callosum. The internal fibers come from the gyrus fornicatus, the internal superior surface of the gyrus frontalis, the upper third of the rolandic convolution and the paracentral and superior parietal gyri. The mesial fibers arise from the external superior surface of the cerebral hemisphere, chiefly from the lower portions of the frontal lobes and partly from the middle third of the rolandic convolution and inferior parietal lobule. For this reason he suggested that a section through the internal and mesial layers might produce a disturbance in gait (interruption of the fibers from the frontal and parietal convolutions) together with psychic alterations, such as apathy and diminished motility.

The fibers of the lower layer come from the gyrus operculi, as well as from the posterior portions of the first and second temporal convolutions and from the island of Reil. On this basis Mingazzini explained the disturbance in taste and hearing.

As early as 1885, Hamilton [33] demonstrated that after crossing in the corpus callosum some of the fibers end in identical and distant areas of the cortex while others are lost in the thalamus and in the internal and external capsules.

Mingazzini [29] showed that some of the callosal fibers originate from the pyramidal cells in the cortex.

Mott and Schaefer [34] were able to demonstrate the presence of motor projection pathways in the corpus callosum by electrical stimulation. Stimulation of the genu apparently provoked movements of the head and neck, and as stimuli approached the splenum the motor responses progressed caudad. The splenium seemed to be devoid of motor components.

32. Seletzky, W., and Gilula, J.: Zur Frage der Funktionen des Balkens bei Tieren, Arch. f. Psychiat. **86**:57, 1928.

33. Hamilton, D.: On the Corpus Callosum in the Adult Human Brain, J. Anat. & Physiol. **19**:385, 1885.

34. Mott, F., and Schaefer, E.: On Movements Resulting from Faradic Excitation of the Corpus Callosum in Monkeys, Brain **13**:174, 1890.

Study of a series of 5 cases of tumor of the corpus callosum by Alpers and Grant [35] indicated that the outstanding symptoms were inability to concentrate and maintain attention; motor signs, such as hemiparesis or weakness of all extremities, and apraxia. It is important to observe, however, that the same symptoms are not present in cases of agenesis.

In this regard, as was emphasized by Armitage and Meagher,[36] positive deductions from the study of patients presenting gross lesions of the corpus callosum may be easily misleading because of the inevitable involvement of neighboring structures. This was particularly true in cases of tumor of the brain. After an extensive study of cases in Cushing's clinic, they could assign no function to the corpus callosum. Moreover, they were unable to detect any apraxia in patients after partial section of the corpus callosum in the midline and found no evidence of disturbance in motor or mental reactions in Macacus rhesus monkeys after complete transection of the commissure.

In 1921, Cameron and Nicholls [37] came to the following conclusion concerning the mental status of patients with agenesis of the corpus callosum:

> Such meagre evidence as we possess seems to indicate that the callosal fibers are of more importance in maintaining and governing the finer co-ordinations of muscular movement in the limbs of the opposite sides than in regulating the higher functions of mentality.

As a result of their work, Kennard and Watts [38] concluded that section of the corpus callosum in monkeys produced no motor weakness and did not cause forced grasping, but did give rise to a definite syndrome characterized by inertia and slowness in initiating purposeful movements. Moreover, section of the corpus callosum subsequent to unilateral lesions of the motor areas produced no additional motor deficit in the contralateral extremities.

These authors found further that a unilateral lesion of the motor or premotor areas subsequent to section of the corpus callosum was followed by no greater deficit than that seen with the same lesion when the corpus callosum was intact. Ipsilateral movement from stimulation of area 6 was not abolished by section of the corpus callosum.

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35. Alpers, B. J., and Grant, F. C.: The Clinical Syndrome of the Corpus Callosum, Arch. Neurol. & Psychiat. **25**:67 (Jan.) 1931.

36. Armitage, G., and Meagher, R.: Gliomas of the Corpus Callosum, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:454, 1933.

37. Cameron, J. L., and Nicholls, A.: Two Rare Abnormalities Occurring in the Same Subject: Partial Absence of the Corpus Callosum; the Stomach Situated Entirely Within the Thorax, Canad. M. A. J. **11**:448, 1921.

38. Kennard, M. A., and Watts, J. W.: Effect of Section of the Corpus Callosum on the Motor Performance of Monkeys, J. Nerv. & Ment. Dis. **79**:159, 1934.

Prior to the introduction of encephalographic diagnosis it was necessary, of course, for the physician to study the patient's mental activity and behavior in retrospect after the postmortem examination had revealed the diagnosis. In this way, in a number of cases, notably those collected by Bruce,[30] a normal condition was reported. From a study of 15 cases reported in the literature and 1 of his own, Bruce concluded that if the brain is otherwise well developed, absence of the corpus callosum does not necessarily produce any disturbance of motility, coordination, general or specific sensibility, reflexes, speech or intelligence.

Cameron stated the opinion[16] that total absence of the corpus callosum is possible without any pathognomonic alteration in the subject's mental or physical capacity.

Dandy[39] divided the corpus callosum in its entire anteroposterior extent and noted no unusual results.

Hartman and Trendelenburg[40] taught both rhesus and Javanese monkeys to perform a complicated series of bimanual movements necessitating the simultaneous use of the two hands in obtaining food. After total section of the corpus callosum these animals showed no evidence of apraxia.

The experiments of Pavlov[41] disclosed that when a reflex, such as the tactile salivary reflex, is conditioned on one side of the body, stimuli applied to corresponding locations on the opposite side of the body produce the same reflex. Division of the corpus callosum by operation abolished the phenomenon entirely; in other words, it is necessary to condition the reflex on the two sides of the body independently.

CLINICAL MANIFESTATIONS

Impaired mentality and epilepsy are the most frequent clinical manifestations associated with agenesis of the corpus callosum. The intellectual status of the patients varies from idiocy to mediocrity. Patients living to an advanced age are, as a rule, of mediocre intelligence. The epileptic seizures may be of the petit mal or of the grand mal type.

The history of a patient with agenesis seldom suggests the function of the corpus callosum, for other anomalies of the brain so becloud the picture that little remains which might be explained by its presence.

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39. Dandy, W. E.: Operative Experience in Cases of Pineal Tumor, Arch. Surg. **33**:19 (July) 1936.

40. Hartman, F., Jr., and Trendelenburg, W.: Zur Frage der Bewegungsstörungen nach Balkendurchtrennung an der Katze und am Affen, Ztschr. f. d. ges. exper. Med. **54**:578, 1927.

41. Pavlov, I.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G. Anrep, London, Oxford University Press, 1926.

In addition to epilepsy and feeblemindedness, spastic paraplegia, nystagmoid movements of the eyes and continued movement of the hands have been reported. As Cameron and others have emphasized, however, defects other than those of the corpus callosum account for the epilepsy and spastic paraplegia in such cases.

All the 3 patients in the cases reported by Davidoff and Dyke [7] suffered from epileptic seizures, and the third patient, a child aged 3 years, was also retarded in mental and physical development. Until she was 19 months old she was unable to walk, and at the age of 3 years she was able to speak only a few words. Their first patient, a child aged 6 years, showed a high average intelligence quotient on the Merrill-Palmer scale.

Of the 5 patients whose cases were reported by Hyndman and Penfield,[8] 4 were epileptic. The patient without epileptic seizures, a boy aged 2 years, was retarded. Not only was he unable to sit up, but he took little or no interest in his surroundings.

In spite of the infrequency of agenesis of the corpus callosum as recorded in the literature, the anomaly probably occurs more often than is thus suggested. This is corroborated by the fact that 3 cases were discovered by Davidoff and Dyke [7] from the 1,100 encephalograms taken during a three year period at the Neurological Institute of New York.[7]

As the use of encephalographic procedures in the study of epileptic and mentally defective persons becomes more frequent, many more cases will be recognized.

REPORT OF A CASE

M. F., a boy aged 9 months, was admitted to the Children's Hospital on Jan. 25, 1938, because of retarded development. Delivery had occurred normally at full term. After birth there was no difficulty with the feedings, but later the child did not seem to progress normally. His parents observed that he was 6 months old before he could hold up his head and about 8 months old before he began to play with toys or made any effort to grab at objects. Recently, although the baby had eaten well, he had failed to gain in weight. At the time of examination, at 9 months, he made no attempt to sit up and was unable to roll over by himself.

Examination.—The child's head was not noticeably high and broad from side to side; the occiput was flat and the frontal bosses prominent (fig. 1 *A*). The anterior fontanel was patent, admitting about one finger tip, but did not indicate increased pressure. The superficial veins over the scalp were somewhat dilated. Examination otherwise disclosed nothing noteworthy except oscillating nystagmus on lateral and upward gaze and the fact that the baby could not sit up and took little interest in his surroundings.

Urinalysis gave normal results. The hemoglobin content of the blood was 75 per cent. There were 4,390,000 erythrocytes and 8,350 leukocytes per cubic millimeter. The Wassermann reaction of the blood was negative. Roentgenograms of the long bones taken during the last three months, as reported by Dr. Rolla G. Karshner, showed osseous development typical of that of a child aged 4 years.

Fig. 1.—Photographs of M. F. at the age of 1 year, taken three months after ventriculographic examination. *A*, lateral view, showing the flatness of the occiput and prominence of the frontal bosses. *B*, anterior view.

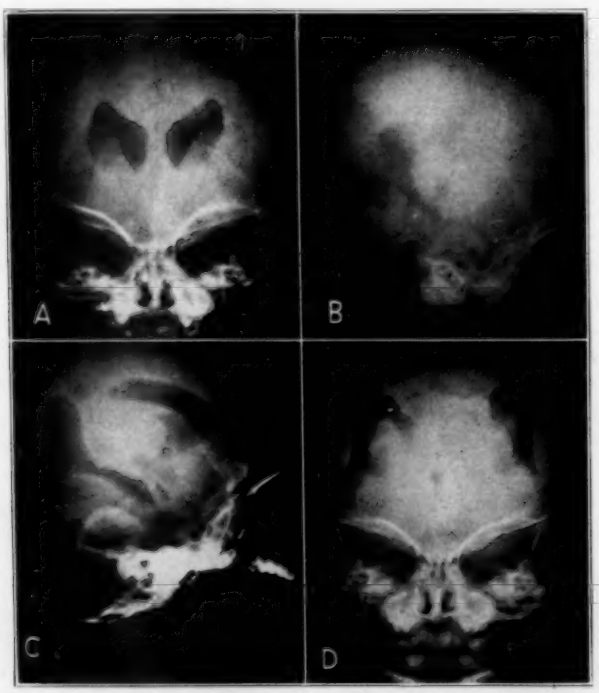

Fig. 2.—*A*, anteroposterior ventriculogram (brow up) showing partial absence of the corpus callosum. The hydrocephalus is evident, and the normally shaped but widely separated lateral ventricles are shown. The third ventricle is not clearly seen, but its vertical extent is increased. *B*, lateral ventriculogram with the occiput up. The dilatation of the posterior horns of the lateral ventricles is demonstrated. *C*, lateral ventriculogram (right side up). The third ventricle appears to extend abnormally high and has a "cocked hat" appearance. The dilatation of the posterior horns is again evident. *D*, posteroanterior view (occiput up). The wide separation of the posterior horns of the lateral ventricles is evident.

The impression after examination at this time was that the patient had hydrocephalus of the communicating type, and pneumographic studies were recommended. The baby had a cold and fever and was sent home until these conditions should subside.

Because of the possibility of increased intracranial pressure and adhesions in the region of the basal cistern, the ventriculographic procedure was felt to be preferable to the encephalographic. The former was carried out, accordingly, on the infant's return to the hospital on February 4.

Approximately 10 cc. of ventricular fluid was withdrawn and 10 cc. of air injected. Roentgenograms were then taken, which revealed a picture which we felt was consistent with a diagnosis of partial agenesis of the corpus callosum.

The filling was fairly adequate. The anteroposterior view disclosed definite hydrocephalus, with normally shaped anterior horns, which, however, were wide apart. The greatest separation of the lateral ventricles was 4.5 cm. The mesial margin of the right ventricle was slightly concave, but not that of the left. Although in this view the third ventricle was not distinct, its vertical extent was 3.5 cm. and its width 0.6 cm. (fig. 2 *A*).

The lateral view, taken with the occiput up, revealed particularly well the marked dilatation of the posterior horns so consistently found in cases of agenesis of the corpus callosum (fig. 2 *B*). The other lateral views also demonstrated this dilatation, but the third ventricle was shown well in only one roentgenogram, in which the abnormal height and "cocked hat" appearance, spoken of by Davidoff and Dyke, seemed to be present (fig. 2 *C*).

The posteroanterior view revealed well the marked separation of the posterior horns of the lateral ventricles (fig. 2 *D*).

DIFFERENTIAL DIAGNOSIS

Cyst of the septum pellucidum, or the so-called fifth ventricle, as described by Dandy,[9] is the one condition likely to be confused with the pneumographic picture of agenesis of the corpus callosum. This is borne out by the fact that in the first cases in the series reported by Davidoff and Dyke and by Hyndman and Penfield the patients were operated on for supposed cysts of the septum pellucidum.

Interestingly, the clinical features of cases of cysts of the septum pellucidum are not unlike those found in cases of agenesis of the corpus callosum. The patients in the 5 cases reported by Verga,[42] in which this cavity was discovered at necropsy, were from psychopathic wards and showed varying degrees of mental disturbance. Another such anomaly, demonstrated to Verga by his friend Sangalli, as cited by Dandy,[9] occurred in a 17 year old girl with epilepsy.

The patients in the cases reported by Gibson [43] and Thompson [44] were psychopathic; in addition, Thompson's patient was judged to be an imbecile.

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42. Verga, A.: Dell' apparato ventricolare del setto lucido e della volta a tre pilastri, Gior. r. Ist. lomb. di sc., 1855, nos. 43 and 44, p. 89; Sul ventriculo della volta a tre pilastri, Gazz. med. ital. lomb. **2**:225, 1851.

43. Gibson, J. K.: A Perforated Septum Pellucidum, Anat. Rec. **28**:103, 1924.

44. Thompson, I. M.: On Certain Abnormal Conditions of the Septum Pellucidum, Univ. California Publ., Anat. **1**:21, 1932.

One of Dandy's [9] patients, a boy aged 4½ years, had a history of retarded development, was mentally backward and suffered from peculiar epileptic attacks, of varying character.

A space-occupying cyst between the lateral ventricles often causes symmetric separation of the anterior horns and bodies of the lateral ventricles, but usually produces mesial excavation as well as separation of the anterior horns. However, unless the cyst communicates with the ventricular system it will not be visualized with air. The characteristic picture of the third ventricle in cases of agenesis of the corpus callosum, then, further establishes the differential diagnosis.

As has been pointed out by Dandy,[9] most cysts of the septum pellucidum which are of unusual size have been observed at necropsy to communicate with the ventricular system by one or more openings into the third and lateral ventricles.

Because of their inconstant position, size and number, and particularly because their borders are ragged and uneven, it is evident that these openings are not preformed, as are the interventricular foramens.

Thompson [44] reviewed the literature on the subject and included the cases of communicating cava.

In cases of communicating cysts of the septum pellucidum, it is possible that ventriculographic examination would reveal a picture similar to that of agenesis of the corpus callosum. The lateral ventricles would be symmetrically separated. A large body of air symmetrically placed and reaching higher than the normal extension of the third ventricle would be shown.

Hyndman and Penfield [8] pointed out that except for a bicornuate appearance of the lateral ventricles, a communicating, enlarged cavum septi pellucidi might well present a picture identical with that of agenesis of the corpus callosum. They concluded, therefore, that the bicornuate appearance of the lateral ventricles is the pathognomonic indication of agenesis of the corpus callosum.

As was emphasized by Davidoff and Dyke,[7] the cardinal encephalographic changes in cases of agenesis of the corpus callosum are (1) marked separation of the lateral ventricles; (2) angular dorsal margins of the lateral ventricles; (3) concave mesial borders of the lateral ventricles; (4) dilatation of the posterior horns of the lateral ventricles; (5) elongation of the interventricular foramens; (6) upward extension and dilatation of the third ventricle, with a "cocked hat" appearance, and (7) radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and their extension through the zone usually occupied by the corpus callosum.

Although a ventricular picture of a communicating cyst of the septum pellucidum might closely simulate that of agenesis of the corpus callosum,

it would without doubt show sufficient variation from the cardinal changes just described to allow a reasonably accurate differential diagnosis to be made.

We feel that the case here reported is one of partial agenesis of the corpus callosum. The lateral ventricles, though abnormally separated, do not, of course, present the upside-down, bicornuate appearance of the lateral ventricles pathognomonic of pronounced agenesis of the corpus callosum. The posterior horns of the lateral ventricles were markedly dilated and separated, and in one view the third ventricle appeared to extend upward and to have the "corset-shaped" or "cocked hat" appearance so often associated with agenesis of the corpus callosum.

Though we believe it to be unlikely, a communicating cyst of the septum pellucidum cannot be entirely excluded in this case.

This infant will be followed with considerable interest. If possible, encephalograms will be taken at later stages of his life. Should death occur and necropsy be performed the certain diagnosis of the congenital anomaly will be established.

SUMMARY

A case presumed to be an instance of partial agenesis of the corpus callosum in a 9 month old infant is reported.

This is the ninth case in which this anomaly has been diagnosed during life by cerebral pneumographic examination, and the diagnosis was made at the earliest age on record.

Roentgenograms of the long bones show development typical of that of a 4 year old child.

The baby shows the developmental retardation often observed in patients with agenesis of the corpus callosum.

Eighteen cases, including the one reported here, have been added to the 82 collected by Baker and Graves in 1933.

REMOVAL OF PROCAINE FROM THE CEREBROSPINAL FLUID DURING ANESTHESIA

H. KOSTER, M.D.

A. SHAPIRO, M.D.

R. WARSHAW, B.A.

AND

M. MARGOLICK, M.D.

BROOKLYN

The duration of spinal anesthesia as ordinarily managed is not affected by any measures undertaken after the anesthetic has once been placed in the subarachnoid space. Studies on the concentration of procaine in the cerebrospinal fluid of patients under spinal anesthesia [1] have shown that after an initial period during which mechanical distribution away from the site of injection takes place there is a gradual disappearance of the procaine from the cerebrospinal fluid. These findings suggested that it might be possible to terminate anesthesia more quickly by removing the procaine from the subarachnoid space.

Adult patients were anesthetized by the subarachnoid injection of 150 mg. of procaine hydrochloride between the second and the third lumbar vertebra, 3.5 cc. of cerebrospinal fluid being used as the solvent.[2] In different patients at various intervals after the initial injection a needle was reinserted at the site of injection and another was inserted into the subarachnoid space three interspaces above. Fluid was allowed to run off freely, and the subarachnoid space was washed out with from three to five successive 10 cc. portions of sterile physiologic solution of sodium chloride. The original fluid and the washings were collected

From the Crown Heights Hospital.

1. Koster, H.; Shapiro, A., and Leikensohn, A.: Procain Concentration Changes at Site of Injection in Subarachnoid Anesthesia, Am. J. Surg. **33**:245-248, 1936; Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection, Arch. Surg. **37**:603-608 (Oct.) 1938. Koster, H.; Shapiro, A., and Warshaw, R.: Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection: Second Report, ibid., to be published.

2. Koster, H.: Spinal Anesthesia, with Special Reference to Its Use in Surgery of the Head, Neck and Thorax, Am. J. Surg. **5**:554-570, 1928.

and measured, and their procaine content was determined photometrically after precipitation with vanillin and potassium mercuric iodide.[3]

In the case of 3 patients no washing was done and fluid was collected only at the site of injection.

Since it had been noticed that pain at the site of the operative wound returns at about the same time that the patient regains voluntary motor power in the legs, the time when the patients were just able to move their legs was determined by frequent trial and used as a reference point for the duration of anesthesia.

Duration of Motor Paralysis After Removal of Procaine

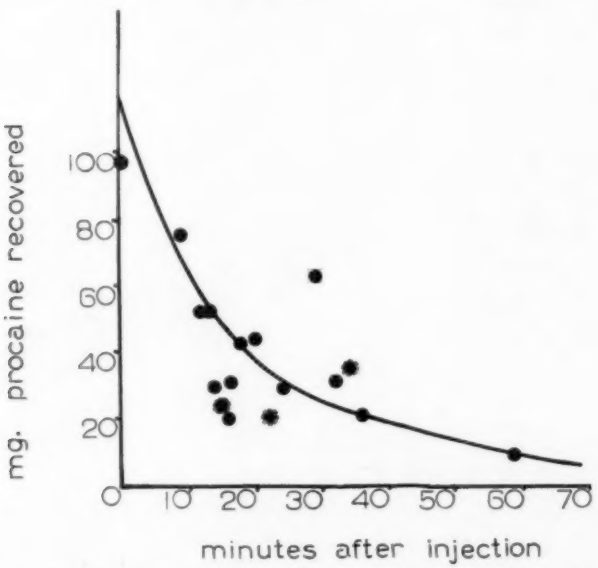
	Time from Injection to Washing, Minutes	Time from Washing to Recovery of Motor Power, Minutes	Time from Injection to Recovery of Motor Power, Minutes
	With Washing		
1	0	0	0
2	9	9	18
3	12	15	27
4	14	11	25
5	16	5	21
6	16	13	29
7	17	12	29
8	18	12	30
9	20	9	29
10	29	4	33
11	35	3	38
12	36	4	40
13	59	2	61
Average	22	7	29
	Without Washing		
1	15	15	30
2	22	25	47
3	31	24	58
Average	24	21	45

It has been observed [1] that motor power in the lower extremities returns about sixty minutes after the subarachnoid injection of 150 mg. of procaine hydrochloride in 3.5 cc. of cerebrospinal fluid. The duration of motor paralysis in patients studied in these experiments is shown in the accompanying table. For 13 patients in whose cases the washing of the subarachnoid space was begun at intervals up to fifty-nine minutes after the initial injection (average twenty-two minutes) the average duration of motor paralysis after the withdrawal of fluid was begun was seven minutes. The average total time from the initial injection to the end of motor paralysis was twenty-nine minutes.

3. Koster, H.; Shapiro, A., and Posen, E.: A Micro Method for the Quantitative Determinations of Procaine in Cerebrospinal Fluid, J. Lab. & Clin. Med. **21**:1096-1098, 1936.

In the 3 cases in which fluid was withdrawn but no washing was performed, the average time to the beginning of withdrawal was twenty-four minutes and the average total duration of motor paralysis was forty-five minutes.

The chart shows the amounts of procaine hydrochloride recovered from the cerebrospinal fluid of different patients at various times after the initial injection. The three points in circles represent samples obtained by simple withdrawal without irrigation. They are included because when spinal fluid and washings were collected separately the procaine content of the washings was less than 10 per cent of the total, a small error in comparison with the experimental scatter.



Amounts of procaine hydrochloride found in the spinal fluid and in washings obtained at various times after the subarachnoid injection of 150 mg. of procaine dissolved in 3.5 cc. of spinal fluid.

Only 100 of the 150 mg. of procaine injected could be recovered when the withdrawal and washing were begun at once. It is evident, therefore, that the ordinates in the chart represent amounts of procaine removable from the cerebrospinal fluid at various times and probably not the total amount of procaine remaining in the subarachnoid space. They must be corrected by a factor of +30 per cent in the early portions and perhaps more in the later portion in order to estimate the total amounts of procaine remaining in the subarachnoid space at various times after injection.

It is of interest also that the simple withdrawal of spinal fluid from a single needle yielded almost as much procaine as could be recovered

by irrigation with saline solution. Irrigation, however, was much more effective in terminating motor paralysis. This may have been due to the dilution of the remaining procaine by saline solution to a concentration below that necessary to maintain motor paralysis.

CONCLUSIONS

1. The duration of paralysis of the lower extremities in spinal anesthesia induced with procaine hydrochloride may be markedly shortened by withdrawing spinal fluid and irrigating the subarachnoid space with physiologic solution of sodium chloride between two needles.

2. When removal and washing are begun immediately after injection of the anesthetic, motor paralysis fails to develop.

3. The amount of procaine recoverable diminishes as the anesthesia progresses.

4. The maximum amount recovered when washing is begun immediately after injection of 150 mg. of procaine hydrochloride is 100 mg.

5. Simple withdrawal is considerably less effective than irrigation in shortening the duration of motor paralysis, even though almost as much procaine is removed by the former method as by the latter.

WARM MOIST AIR THERAPY FOR BURNS

SIDNEY SMITH, M.S.

ROY RISK, M.D.†

AND

CHARLES BECK, M.S.

CHICAGO

The subject of wound healing of all types was thoroughly reviewed by Arey in 1936.

Modern therapy for burns attempts to alleviate the subsequent toxemia and secondary shock of severe burns by rendering any supposed toxins arising from the heat-killed tissue insoluble. For many reasons, the conditions for healing under the coagulum of chemically coalesced debris do not approach the optimum conditions existing under the natural fibrin eschar (Carrel; Carrel and Baker [1]).

The possibility of obtaining more rapid healing by providing a more nearly ideal physiologic environment for the wounded area led to the following study on rats, in which a comparative evaluation of various therapeutic agents and methods used as controls has been undertaken.

METHOD

An experimental humidity chamber with a wood frame and glass windows, measuring 6 feet (180 cm.) long, 3 feet (90 cm.) wide and 3 feet (90 cm.) high, with a displacement of 54 cubic feet (153 cubic meters), was built. Air and atomized water were mixed and heated to 250 C., which killed any micro-organisms present in the mixture. The air-steam mixture, thermostatically controlled, was then cooled to 90 F., which permitted the excess water to precipitate out and insured saturation of the air. This sterile and moisture-laden air was then forced into the chamber at the rate of 200 cubic feet (566 cubic meters) per minute or, roughly, four complete changes of air per minute. The chamber was equipped with a false bottom which permitted daily cleaning.

Studies by Smith and Moise,[2] Sauerbruch [3] (on man), Carrel and Baker,[1b] Osborne and Mendel,[4] Herrmannsdorfer [5] (on man), Harvey and Howes [6] and

† Dr. Risk died March 21, 1938.

From the Physiological Laboratories, the University of Chicago.

1. (*a*) Carrel, A.: Leukocytic Trephones, J. A. M. A. **82**:255-259 (Jan. 26) 1924. (*b*) Carrel, A., and Baker, L. E.: J. Exper. Med. **44**:503, 1926.
2. Smith, A. H., and Moise, T. S.: J. Exper. Med. **40**:209, 1924.
3. Sauerbruch, F.: München. med. Wchnschr. **71**:1299, 1924.
4. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **69**:661, 1927.
5. Herrmannsdorfer, A.: Deutsche Ztschr. f. Chir. **200**:534, 1927.
6. Harvey, S. C., and Howes, E. L.: Ann. Surg. **91**:641, 1930.

Reimers and Winkler [7] indicated that a high protein diet accelerates wound healing, whereas a high carbohydrate, fat or vegetable diet markedly inhibits repair. The diet which seemed most satisfactory for this experiment consisted of raw meat, malted milk and a commercially prepared mixture (Purina fox chow [7a]). An excess of food and water was kept in both the experimental and the control cages at all times.

The lesions were produced by a brass branding iron 10.8 cm. square, weighing 240 Gm. and heated to the temperature of boiling castor oil (240 C.). The iron was placed on the shaven back of the etherized rat for 20 seconds at constant pressure (the weight of the iron). The heat penetrated the corium, producing a third degree burn.

The rats, all mature and weighing about 280 Gm., were then divided into two sets. One set was placed in the humidity chamber (box) while the other was placed in standard wire false bottom cages at room temperature and treated

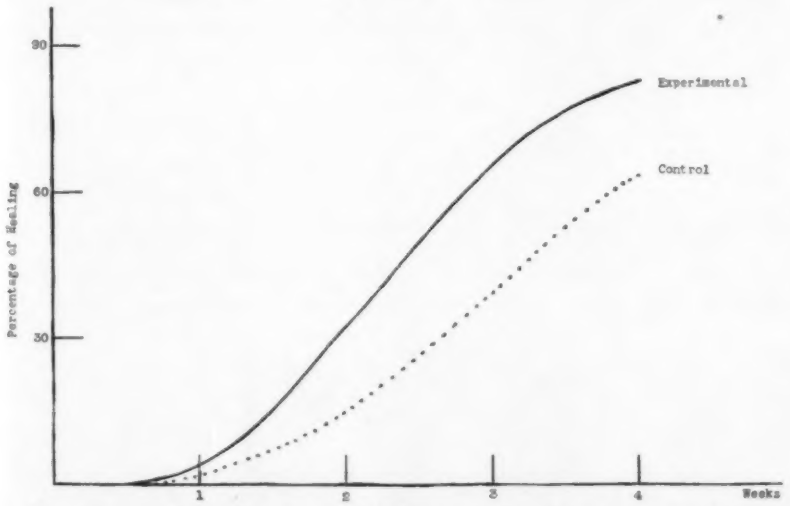


Fig. 1 (experiment 1).—Rate of healing of deep cutaneous burns in 10 experimental and 7 control rats treated with butesin picrate ointment three times daily.

in several ways, generally acceptable to the members of the medical profession. The two groups were designated respectively as the experimental and the control set.

RESULTS

Figure 1 indicates the comparative rates of healing based on averaged biweekly measurements of the reduction of the injured area. Owing to the presence of debris and coagulum in the controls, healing for the first week cannot be measured accurately. (The percentile rate of healing [ordinate] is plotted against time in

7. Reimers, C., and Winkler, H.: Deutsche Ztschr. f. Chir. **241**:313, 1933.

7a. Purina fox chow is composed of the following ingredients: Carotene, dried meat, corn grits, alfalfa meal, ground oat groats, wheat germ, barley, malt, molasses, dried skim milk, 1 per cent iodized salt and cod liver oil. Guaranteed analysis: protein, 20 per cent (not less); fat, 3 per cent (not less); fiber, 6 per cent (not more); nitrogen-free extract, 46 per cent.

weeks [abscissa]). The experiment was terminated at the beginning of the fourth week, when the experimental rats, which received no other therapy than the heat and humidity of the box, were 82 per cent healed. The control rats, treated with butesin picrate ointment three times daily during the same period, were 63 per cent healed, a difference of 19 per cent in favor of the warmth and humidity.

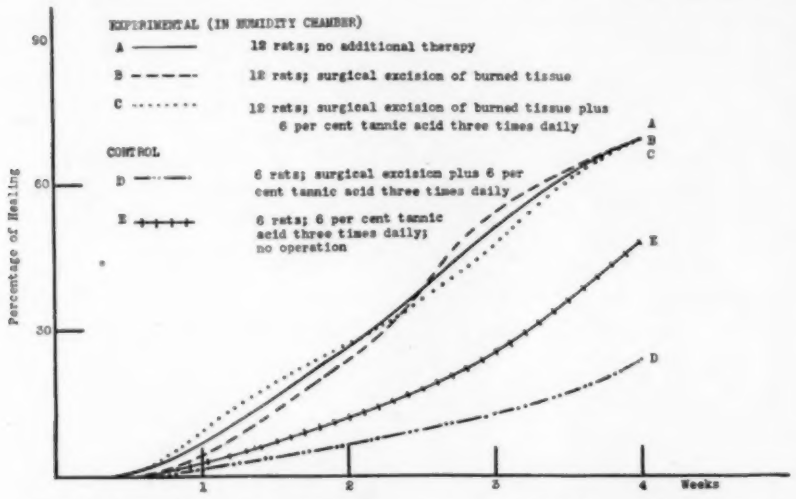


Fig. 2 (experiment 2).—Comparative rates of healing with different types of therapy.

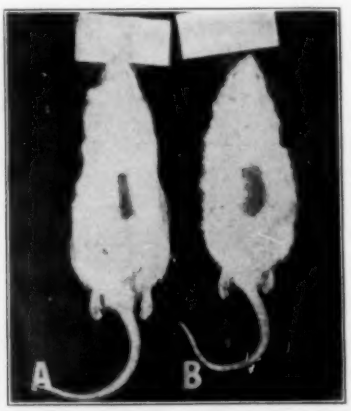


Fig. 3.—*A*, experimental rat treated with surgical excision of the burned tissue plus heat and humidity; *B*, control rat treated with surgical excision of the burned tissue and no other therapy.

Figure 2 illustrates the comparative rate of healing for rats when tannic acid therapy alone and surgical excision of debris plus application of tannic acid were used on groups in both the experimental and the control set.

In this study groups A, B and C composed the experimental set and groups D and E the control set. Group A received no additional therapy. In group B the

burned tissue was surgically excised. In groups C and D the burned tissue was excised and 6 per cent tannic acid used three times daily. Group E received the tannic acid treatment without the surgical excision. Despite the variation in the additional therapy used on the various animals in the experimental set, all rats at the fourth week were 70 per cent healed, in contrast to the two control groups; the rats in group D, which received 6 per cent tannic acid three times daily in addition to surgical excision of the debris, were 24 per cent healed, and those in group E, receiving 6 per cent tannic acid three times daily but without surgical excision of the debris, were 48 per cent healed.

It would seem from these data that surgical excision and surgical excision plus application of tannic acid, when used in conjunction with warmth and humidity, provide no additional stimulus to repair. It does seem that in the case of the control rats the use of tannic acid alone was better therapy than surgical removal of the debris followed by spraying with tannic acid.

Figure 3 illustrates the comparative rates of healing in the experimental and in the control rats when the burned area was surgically excised and no additional therapy given.

COMMENT

Among the many physiologic factors which might account for these results may be listed the following:

1. Healing processes are markedly slowed in the presence of debris (Bauer;[8] Hauberisser;[9] Dressel[10]). In the humidity chamber the moisture of the air kept the entire body wet, and this soaking action softened the debris, which was sloughed off the wound or picked off by the rats within the first five days.

2. Increase of local temperature by thermal application increases the rate of healing in rats (Fuke[11]). Ebeling,[12] using the alligator, made the same observation. In the humidity chamber the warmth provided exceeded the normal temperature of the skin.

3. Epithelial proliferation is faster in the presence of moisture (Burrows,[13] 1924). The saturated air of the humidity chamber not only provides moisture but permits retention of water, for evaporation is minimal in saturated air.

4. Chief among the many factors that delay wound healing is infection (Carrel; Kiser[14]). According to a report by Schade and Claussen,[15] the p_H of tissue may be a prime factor in the incidence of pathogenic invasion. These investigators, working with the quinhydrone electrode, found that healthy granulating tissue had a p_H of 5.6 but that if the

8. Bauer, K. H.: Arch. f. klin. Chir. **163**:564, 1931.
9. Hauberisser, E.: Beitr. z. klin. Chir. **153**:257, 1931.
10. Footnote deleted on proof.
11. Fuke, T.: Jap. J. Obst. & Gynec. **15**:234, 1932.
12. Ebeling, A. H.: J. Exper. Med. **35**:657, 1922.
13. Burrows, M. T.: J. M. Research **44**:615, 1924.
14. Kiser, S.: Arch. f. klin. Chir. **149**:146, 1927.
15. Schade, H., and Claussen, F.: München. med. Wchnschr. **73**:343, 1926.

tissue became dry the p_H rose to 8.3. If the alkalinity persisted, infection and sloughing occurred. Reimers and Winkler [7] reported that carbon dioxide escapes from the surface of wounded tissue thirty times as fast as from uninjured skin. The fact that Reimers and Winkler reported a rising p_H coinciding with drying of the tissue suggests the possibility that moisture may act as a vehicle in the retention of the acid radicals responsible for the lowered p_H.

As for the tannic acid or butesin picrate ointment, we believe on the basis of the evidence obtained in experiment 2 that these substances possess no specific accelerative healing action. It would seem that their main function is to provide an insoluble coagulant over the wound. The incidence of infection under the coagulant produced by tannic acid has been reported many times and constitutes the chief objection to the use of the medicament.[16]

SUMMARY

Deep cutaneous burns were inflicted on etherized rats. Studies of recovery with various types of therapy or lack of therapy were undertaken. The speed of healing constituted the criterion of recovery. The results of the experiments were as follows:

1. The cutaneous burns of rats receiving the warm moist air therapy healed faster than those of controls living in ordinary air at room temperature, even when the controls received in addition typical treatments with well known therapeutic agents (butesin picrate and tannic acid).

2. The use of tannic acid and surgical excision in addition to the warm moist air therapy did not produce significant differences in the rate of healing in the experimental rats.

3. Surgical excision of the debris in the control group of rats was better than no therapy but was inferior to the chemical coagulants present in tannic acid or butesin picrate ointment.

Dr. A. J. Carlson gave assistance and criticism in this work.

16. Turner, A. C.: Contribution to Treatment of Burns, Brit. M. J. **2**:995 (Nov. 23) 1935. Taylor, F.: Misuse of Tannic Acid, J. A. M. A. **106**:1144-1146 (April 4) 1936.